Textbook of Histology

TEXTBOOK OF HISTOLOGY

by JOSÉ F. NONIDEZ, D.:

Late Professor of Anatomy, Cornell
and Professor of Microscopic Anatomy, University of Georgia

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Professor of Anatomy, University of Pennsylvania

With 287 illustrations, composed of 209
drawings and diagrams and 193 photomicrographs

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Preface

Professor Nonidez had been working for some time
and manuscript of a textbook of histology when he died in the fall of
1947, only a few weeks after his arrival at the University of Georgia. His
original intention was to deal only with the fundamental tissues and to
this end he prepared original drawings with his own hand. A short time
before his death, he decided to expand the work to include microscopic
anatomy of the various organs, and he began to make drawings for the
new chapters. The following statements from his preliminary preface in-
dicate his objectives.

"The purpose of the proposed book is to present in concise form the
fundamental facts on the finer structure of the mammalian body, includ-
ing man, and to emphasize as far as possible the functional aspects. . . .
It was soon realized that a book with a concise text would have to be
adequately illustrated and that figures would fit the text better if they
were drawn for the purpose instead of being borrowed from other text-
books and scientific journals. . . . In preparing the text, it has been
borne in mind that the inclusion of controversial subjects, names of au-
thors, and references make reading difficult. . . . Many students lack
proper preparation for the study of histology. This situation has been
taken into account, and little knowledge of anatomy and physiology is
taken for granted."

When, at Christmas time, 1947, I assumed the task of completing the
work so admirably begun by Professor Nonidez, the fundamental plan
appealed to me and I decided to follow it as closely as possible. In the
main, this has been done, although the final result is quite different from
that which would have come from Professor Nonidez's pen.

Work on the project was undertaken with the thought that a textbook
should contain selections and illustrations from its subject, should sum-
marize where summarization is possible without jeopardizing significant
meaning, should emphasize items of especial importance according to

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those of the last four chapters, were made by Mr. Adolph Marfang, to whom I am greatly indebted for skillful completion of a task under difficult conditions.

Nearly all photomicrographs were made with Leitz and Zeiss lenses and with the Fish-Schurman Zirconarc illuminator. A special effort has been made to use as few magnifications as possible for the illustrations and to keep them consistent throughout (except in the case of very low powers). I have estimated the magnifications of most drawings by comparing them with the few of known magnification. The majority of the photomicrographs are reproduced at 1200 ×, 600 ×, 300 ×, and 150 ×, although it proved expedient to use other magnifications in a few instances.

The microscopic specimens came from many sources, mainly from the collections of the University of Pennsylvania, but a few from the University of Washington, Northwestern University, University of Louisville, and Denison University. Unless indicated otherwise, they are stained with hematoxylin and eosin. Some remarkable slides were prepared more than fifty years ago by or for the late Professor George A. Piersol. A few of the latter were formerly used for drawings in his textbook. To my friends and colleagues, Professors L. B. Arey, S. I. Kornhauser, W. H. F. Addison, Balduin Lucké, A. J. Ramsay, S. C. Williams, Mary J. Hogue, R F. Becker, Dr. L. L. Caulkins, Dr. Q. B. DeMarsh, Mr. James Rankin, and Miss Ann Tatum, I am indebted for a number of fine preparations.

I am appreciative of the assistance of a number of people who put aside other tasks to help speed this one to completion. The departmental secretaries, Thalia Gilliam and Alice Busbar, deserve praise for skillful preparation of the manuscript and editorial assistance with it. The careful editing by my wife has removed many of my own hurried errors. My colleagues in the Department of Anatomy at the University of Pennsylvania contributed many valuable suggestions. Three who read the manuscript critically are Dr. William Chambers, Dr. Ruth Koenig, and Dr. Harold Koenig.

WILLIAM F. WINDLE

Philadelphia, Pennsylvania
February, 1949

the opinions of the authors, and should elicit abiding interest of the reader—at least, the more serious student reader. Many of the available histology books have grown with the years, as, indeed, has knowledge of the subject, and now present the beginner with more details than he can master without encroachment on time needed for other subjects, or needed for consultation of other sources of information in this subject. Some other histology books are too attenuated or are inadequately illustrated for all classes.

The present textbook is for the beginner. As it is not intended for a reference book, many details are lacking. In the more complete treatises listed in a brief bibliography at the end will be found a great mass of supplementary information. Furthermore, those books contain extensive bibliographic references to original articles and monographs on many subjects. A comparable bibliography will not be found in the present textbook. It is only the exceptional student who makes any use of long lists of references cited in the principal textbooks of histology. In the present textbook, I have experimented with the use of selected annotated references for collateral reading in the generally available textbooks, monographs, and scientific journals. I hope that these will guide many students to more advanced treatises on histology.

Another new feature of the book is a reference list of motion-picture films. These are visual aids found useful in the course which I teach, as supplements to lectures and informal microprojection conferences.

Professor Nonidez left rough copy for most of the chapters on the fundamental tissues, the blood vessels, and the tubular digestive organs. At first, an effort was made to incorporate as much of his writing as possible, while constructing a coherent descriptive account of histology. This proved difficult and was dropped to save time and promote coherence. The final copy has been so altered that all responsibility for mistakes and inadequacies must be charged directly to me. Furthermore, I have changed the organizational plan and have not divided the subject into histology proper and microscopic anatomy because it seems that such a division is, at best, quite arbitrary and artificial.

A great majority of Professor Nonidez's drawings have been used, and several new copies of diagrams from other sources, prepared by my daughter, have been added. Only two of the photomicrographs included are by Professor Nonidez. Most of the photomicrographs were taken by Mr. Basil B. Varian, whose sudden death during this task was a grievous loss to all his friends and colleagues. Other photomicrographs, mainly

those of the last four chapters, were made by Mr. Adolph Marfang, to whom I am greatly indebted for skillful completion of a task under difficult conditions.

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Contents

Tissues and Methods for Their Study

Histology is the study of the minute structure of the body. With the aid of the microscope, it extends the horizon of anatomy. Histology gives insight into the functioning of tissues and organs and provides a basis for general and cellular physiology. Histology is a fascinating study of the fabric of which your body is constructed.

TISSUES

Five main kinds of tissue make up the body. The protective sheets of cells covering surfaces or lining cavities constitute **epithelial tissue.** The circulating cell-containing fluid within vascular channels may be considered a tissue, the **blood.** The highly fibrous and only slightly cellular supporting, connecting, and padding materials including bones, cartilages, tendons, and fat are collectively designated **connective tissue.** The elongated elements that are concerned with contraction form **muscular tissue.** Collections of cells with long processes specialized for reception of stimuli and conduction of impulses, together with other developmentally related elements, build **nervous tissue.**

These are rather arbitrary divisions, for no tissue exists in pure form. Epithelium contains nerves. Connective tissue has nerves and blood in vessels. Muscular tissue could not function without both of these, plus connective-tissue sheaths. Even blood has in it cells that properly belong to another tissue. We can discuss each separately but must bear in mind that all are interdependent. Thus, consideration of such a component of the body as a muscle can be divided into the **histology** of its principal component (muscular tissue in this instance) and the **microscopic anatomy** of it as an organ performing a certain function by the interaction of all its tissues.

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The interstitial fluid is not present in like amounts in all tissues. An imperceptible quantity occurs in such highly cellular tissue as epithelium. Although considerable tissue fluid resides in connective tissues, it is crowded by fibers and solid matrix substances in tendons, cartilages, and bones. In a few locations, it is free and has been given specific names. In this category are cerebrospinal fluid, aqueous humor of the eye, pleural

FIGURE 1. Schematic diagram of the divisions of the body fluids and their proportion of the total body weight. Redrawn from J. R. Elkinton, in Howell's Textbook of Physiology, J. F. Fulton, editor, Saunders, 1947.

and peritoneal fluids, and the synovial fluid of joints. Some of the interstitial fluid is contained within a closed system, the thin-walled lymphatic vessels that are found in most tissues of the body.

Two membranes are interposed in the passage of fluid from blood into the tissues and back to blood. These are the linings of blood capillaries and lymphatic capillaries. Only the vascular lining cells and the blood cells themselves can be nourished and supplied with oxygen directly from plasma. Other cells are reached by transport of these substances through tissue fluid.

Two useful terms to add to your vocabulary now are **parenchyma** and **stroma**. In our example, the parenchyma is muscular tissue and the stroma is the connective tissue holding functional elements apart and forming a framework over which nerves and vessels can reach them.

At the beginning of a study of histology, it is proper to inquire about the components of tissues. Naturally, your attention will at first focus upon the **cell**, especially the cell that has been killed, dehydrated, and beautifully although artificially colored. Do not let the artistic qualities of your histological preparations divert your thoughts from the other components, which are the noncellular **interstitial matrix** substances, including such formed elements as fibers, and the **interstitial fluid**. This fluid, especially, is apt to be neglected. It is water, with many organic and inorganic salts dissolved in it; and watery solutions cannot be seen through a microscope. However, the role of water in the structure of the body is fundamental, and no true appreciation of functional histology is possible without some consideration of the body fluids.

FLUIDS

Although water makes up approximately 70 per cent of the body, the amount varies in different tissues and organs. The fluid of the body may be thought of as occupying two compartments: the cell and the intercellular spaces. Fluid in the cell, the **intracellular fluid**, is quite different chemically from the fluids of the spaces outside the cell, the interstitial fluid or **tissue fluid** and the **plasma** of the blood. Potassium, phosphate, and protein ions in the intracellular fluid take the place of sodium and chlorine ions of the extracellular fluids. The two major fluid compartments are separated from each other by the **cell membrane** through which water and certain substances in solution can pass.

The source of all body fluids is food and water entering the digestive tract. Water and other components of the body fluids can leave again through the epithelium lining the stomach and intestines, lungs, kidneys (some reabsorption here), and skin. The quantities that enter and leave the body vary widely with changing conditions of the external environment and with metabolism. The quantities of the fluids within the healthy body remain remarkably constant at all times. Plasma forms about 5 per cent, tissue fluid 15 per cent, and intracellular fluid 50 per cent of the weight of the body of an adult man. These relationships are diagrammatically illustrated in Fig. 1.

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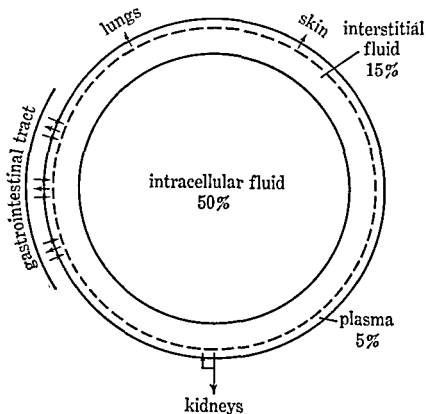

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From what has been said, we hope it is clear that the body is formed very largely of water, which serves as the medium for all its physiological processes. Within the intracellular fluid take place the vital reactions that constitute life. The extracellular fluids provide an environment for the cells and a liaison with the outer world. Terrestrial life became possible because the organism was able to find a means of maintaining a constant environment for life processes of its cells irrespective of most external changes. The secret of man's adaptability to adverse surroundings is to be found very largely in the constancy of the internal environment of his protoplasm. Let us leave consideration of the body fluids for the time being with the often quoted declaration of the great physiologist, Claude Bernard, that "all vital mechanisms, however varied they may be, have but one object, that of preserving constant the conditions of life in the internal environment."

METHODS

Chemical methods for determining the composition of tissues and the physiological methods of investigating their function can be left for future courses. Your present concern is with visualization of the structural organization of tissues, not so much as a means of their identification when you encounter them again in pathology, as to help you build a concept of the living organism that is prerequisite for any rational understanding of yourself. The question is how to proceed so that you may come away with the truest picture.

To know the living organism, you must study it alive. However, there are limitations to any such proposal, especially so for the beginning student of histology, lacking the facilities of research institutes. If only you could put transparent windows in the living animal and bring your microscope to focus upon his tissues! You probably cannot do such an experiment, but there is no reason why you cannot have the benefit of others' observations by this technique, for motion pictures of living intact tissues taken through the microscope are available.[1]

The next best procedure would be to remove tiny pieces of living tissue from animals or man and culture them, as the bacteriologist grows microorganisms, in an appropriate medium or in the anterior chamber of an animal's eye behind the transparent cornea. These techniques require special training and equipment, too. But, again, you can observe cinephotomicrographs of results obtained by tissue-culture techniques. In

[1] See Visual Aids, p. 435.

taking the sort of pictures in question, time was allowed to elapse between each frame's exposure. Consequently the activities of cells in tissue cultures will be speeded up in the projection. Time-lapse motion pictures of living cells are invaluable aids to understanding functional histology.

Anyone can remove bits of tissue from freshly killed animals, tease them with needles in a drop of physiological saline solution on a slide, and study them with the aid of the compound microscope. For that matter, you can obtain tissues from your own body, such as scrapings of epithelium from the mouth or drops of fresh blood from the finger. This is a very good way to begin a study of fresh and living cells. You will note that cells do not die at once upon removal from their normal habitat, nor do they all die at the time of death of the organism of which they are components. Some cells, when removed as long as forty-eight hours after death of human fetuses, have been grown in culture tubes.

The darkfield microscope and the phase-difference microscope are important adjuncts to a study of living tissues. Certain dyes can be added without harm to tissues removed from the body for microscopical study. This is spoken of as **supravital staining.** Tissues can also be stained by introducing dye solutions into the living organism. This constitutes **vital staining.** Such procedures bring out structural details not readily seen in unstained living cells with ordinary brightfield microscopes. The study of living and fresh surviving tissues should be a part of every course in histology, but it will not supplant the use of prepared slides of stained dead and dehydrated tissues. Even though it occupies only a small fraction of your time, observation of fresh tissue should lead to a truer interpretation of the visual impressions to be gained from prepared specimens, study of which will take most of your time.

The preparation of sections of tissues and organs for study under the compound microscope, known as **histological technique,** requires some skill and much time. Methods are varied and complex. They are fully described in treatises devoted to that subject. It is doubtful if any word picture, even of the more common procedures employed to make stained microscope slides out of pieces of fresh organs, can substitute for first-hand observation of the process. It is hoped that demonstrations will be available for any student lacking such knowledge. The instructor usually assumes that you know something about the processes. If you do not understand, ask him.

Reduced to barest essentials, the technique is as follows: (1) Tissues are killed or "fixed" by subjecting them to the action of protoplasm-

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[1] See Visual Aids, p. 435.

Cells, Living Components of Tissues

To know the whole, one must understand the parts of which it is made. Cells are the structural and functional units of the body. In simplest form, the animal cell is a spherical body of living material called **protoplasm**. It is not a formless mass like a globule of wet gelatin, for it has certain well-defined structures within it. The most conspicuous of these is the **nucleus**. The protoplasm around the nucleus is the **cytoplasm**.

Within the cytoplasm are many things, none very easy to see. A minute body, known as a centrosome, is visible at the time of cell division. It and other little structures, believed to be concerned with more or less specific functional activities, have been designated **organoids**. Special techniques are usually required to demonstrate them. Routine preparations of tissues almost never reveal them. Other minute objects, more readily observed, are **cytoplasmic inclusions,** such as granules or droplets of one kind or another.

Many of the organoids and inclusions are indicated very diagrammatically in Fig. 2, a fantastic picture of a cell, such as never actually exists in any mammalian tissue, although some unicellular animalcules present even more surprising appearances. The picture is a map, not a portrait. Contrast it with photographs of living cells in Figs. 3 and 9C.

PROTOPLASM

Protoplasm is a chemical organization of organic and inorganic compounds in a fluid medium forming a vital system. Its high water content accounts for the great total quantity of intracellular fluid. Protoplasm is a substance of complex and, indeed, perplexing organization. The histologist has not been able to understand it; neither has the biochemist.

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coagulating chemical solutions. Rapidity of action is essential; perfusion through vascular channels is preferable to immersion of pieces. (2) Water is removed from them with alcohol and, through an intermediate solvent, they are infiltrated with some material, like paraffin or collodion, that will solidify to form blocks containing the tissues. (3) Slices as thin as 2 to 5 μ, but usually 10 μ or more, are shaved from these blocks with a precision cutting machine, called a **microtome**. (4) These slices or sections of tissues are stained either before or after being affixed to glass slides. Staining is done with a great variety of dyes or with certain metallic salts, chiefly silver. Some components of cells, notably nuclear chromatin, are said to be basophilic because they have affinity for **basic dyes**, such as hematoxylin. Other components of cells and intercellular substances are acidophilic and stain with the **acid dyes**, like eosin. (5) The stained slices are rendered transparent with oils or solvents, such as xylol. They are finally covered with a drop of transparent mounting medium having nearly the same refractive index as the glass slide and cover slip between which they are preserved.

After all of this, it is surprising that the final preparation bears as close a resemblance to living tissue as it does. We can be sure that standardized procedures, properly controlled, will constantly give uniform results which we can interpret in terms of living tissues.

REFERENCES

1. Elkinton, J. R.: Physiology of Body Fluids, being Chap. 43, pp. 935–963, in *Howell's Textbook of Physiology*, 15th ed., J. F. Fulton, editor; Philadelphia, W. B. Saunders Company, 1947.
   This is a good recent summarizing article on fluids of the body. Much of it is too advanced for a beginner, who is advised to omit the parts in fine print; the first ten pages are recommended. A valuable series of references will be found at the end; note particularly numbers 34, 38, 48, and 50.

2. Cowdry, E. V.: Ageing of Tissue Fluids, being Chap. 23, pp. 583–625, in *Problems of Ageing*, 2d ed., E. V. Cowdry, editor; Baltimore, The Williams & Wilkins Company, 1942.
   This is a rather long article, but eminently worth while. Come back and read it when you have studied all the fundamental tissues. Do not fail to do this.

3. Guyer, M. F.: *Animal Microscopy*, 4th ed.; Chicago, University of Chicago Press, 1936.
   For those who want to learn the methods of histological technique, this is a general elementary book. There is no need to read all of it, but a little time spent in glancing through it will help you.
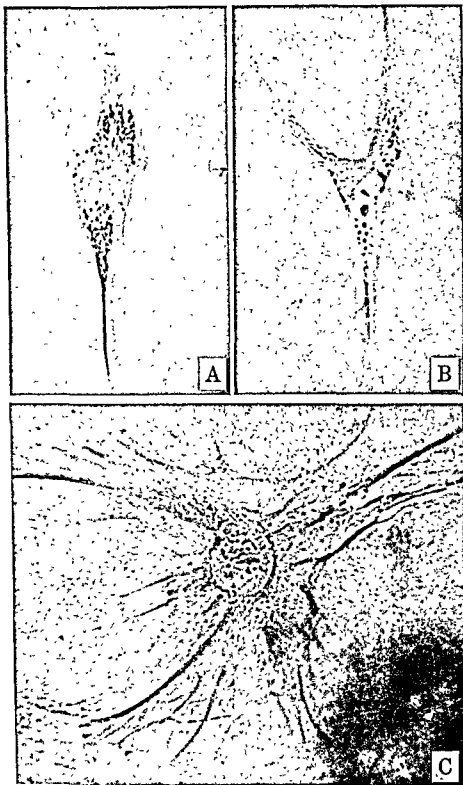
FIGURE 3 Living cells in tissue cultures as seen with Spencer phase microscope: *A*
and *B*, fibroblasts of chick embryo heart containing brilliant fat droplets and less brilliant granules of other substances; *C*, large cell from human fetal cerebellum. Specimens from Drs. Mary Jane Hogue and S. C. Williams. Photomicrograph, 600 ×.

However, the two working together are beginning to break down its mysteries. Cytochemistry is a promising new science but beyond the scope of the present book.

It is, perhaps, sufficient to say that the components of protoplasm are associated and combined in such a manner that the resulting complex is
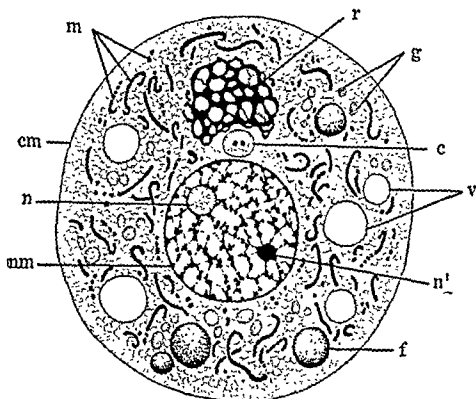

FIGURE 2. Diagram of an animal cell in which many inclusions and organoids are simultaneously presented: c, centrosome, cm, cell membrane; f, fat droplet; g, glycogen, m, mitochondria; n, nucleolus; n', karyosome; nm, nuclear membrane; r, internal reticular apparatus (Golgi); v, vacuoles.

endowed with characteristics that constitute life. Among these are irritability, conductivity, contractility, and metabolism resulting in growth. These properties of protoplasm have been preserved through the ages because it has the capacity to reproduce and give rise to protoplasmic units like itself. The fundamental properties are common to almost all cells, but in the course of evolution, protoplasmic changes have occurred. These changes have led to the great variety of plants and animals that inhabit the earth today.

If you wish to study protoplasm, you will have to study it in the cell, for it is not a substance that can be collected in beakers and examined in large quantities. It functions only when compartmentalized. Further-

fluid droplets or particulate matter, phenomena known as **pinocytosis** and **phagocytosis**, are beautifully portrayed in motion pictures. However, the greatest show is cell division and especially early cleavage of mammalian egg cells. No series of drawings or even photographs can substitute for these.

FIXED AND STAINED CELLS

Only a limited amount of class time can be spent with living cells. It is essential and desirable to study preparations of fixed and stained tissues.
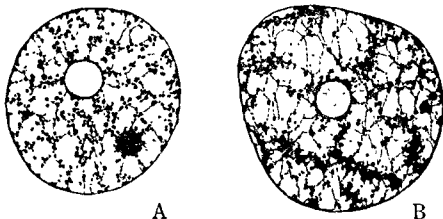

FIGURE 4 Structure of the nucleus: A, spinal ganglion cell (pig) and, B, oocyte (cat), showing large homogeneous nucleoli and chromatin on linin networks. A karyosome is seen in A 1800 ×.

Therefore, let us look at some of the component cells of prepared tissues and try to learn as much as possible.

What do stained histological sections reveal? The usual procedure, using hematoxylin and eosin to stain the tissues, colors the cell cytoplasm pink (eosin) and nucleus blue (hematoxylin). Most extracellular structures, e.g., connective-tissue fibers, are pink, too. There are exceptions to these generalizations. Sometimes the cytoplasm contains blue-staining material. But, by and large, your preparations will show pink cells with blue nuclei; and you will not see all the organoids and inclusions in the cytoplasm. It is necessary to use a number of special staining methods to reveal mitochondria, internal reticular apparatus, neurofibrils, etc. Favorably selected material, expertly stained, does reveal many details of cytology that deserve more than passing mention, but first you should attend to the major structures

Nucleus· The nucleus of fixed and stained cells appears typically as a spheroid, or it may be elongated, as in tall cells, or misshapen by com-

more, it is a substance that is inadequately understood when studied only in fixed and stained cells in which chemical coagulation has produced artifacts. Comparison of fixed and stained protoplasm with that of surviving or truly living and functioning cells will provide an opportunity to understand life processes.

LIVING CELLS

There are limitations to the study of living cells, and you will not be able to see all details of structure described by investigators who have unlimited time, patience, and facilities at their disposal. Nevertheless, if you progress no further than examination of fresh blood, you will be able to watch living and moving white blood cells and see in them some of the structures to be mentioned here. Motion-picture demonstrations of living cells reveal other interesting details, not so much those of structure as those of function.

With your own microscope, you may see the nucleus of the living cell, because its light-refracting power is different from that of the cytoplasm. You may be able to distinguish cytoplasmic particles that represent inclusions. The specific granules of leucocytes are possible to see. You will appreciate the existence of a nuclear membrane and of a cell boundary. Aside from these things, do not expect to observe much structural detail in living cells with the ordinary compound microscope. Time-lapse motion-picture photographs of cells reveal a few other details. Darkfield and phase microscopy add greatly to observation of the components of living cells.

During cell division you will see chromosomes as well as parts of the astral body (Fig. 9C). You can easily observe mitochondria, far better in fact with the phase microscope than you will ever be able to see them in stained sections. Look for fibrils in nerve cells, specific granules in leucocytes, and secretion droplets in gland cells. Supravital and vital staining are procedures that aid considerably in visualizing intracellular structures with the ordinary brightfield microscope.

The principal value of studying living cells is to demonstrate functional rather than structural details. Motility of living cells can be seen in your own white blood corpuscles, even better in motion pictures. The several varieties of corpuscles exhibit different kinds of movement, but it is always slow movement. Remember that it is speeded greatly in the time-lapse motion pictures. Other cell activities, including the engulfing of

to identify cell types and distinguish one type from another. Some variations are illustrated in Fig. 5. A wide range in size of nuclei is also encountered in the body, as may be seen in this same figure. The largest
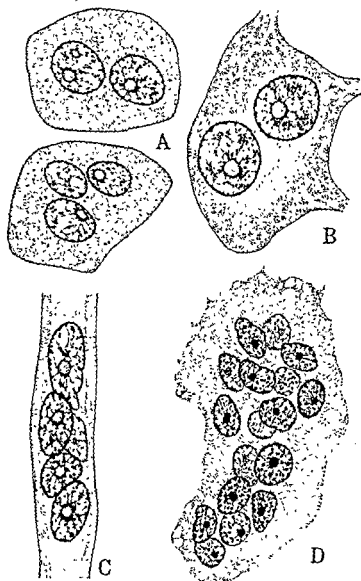
FIGURE 6 Examples of multinucleated cells: A, human liver; B, autonomic ganglion of rabbit, C, myoblast of cat fetus, D, osteoclast of cat fetus 1200 ×

nuclei are found in certain giant cells, in sex cells, and in large nerve cells; the smallest, in lymphocytes and in small nerve cells Some big nuclei occupy relatively less space in their cells than do many very small nuclei.

There is typically but one nucleus, although binucleated cells are often encountered in liver, bladder. and sympathetic ganglia, and multinucle-

pression. In its clear background is a delicate meshwork of *linin threads* on which are arranged smaller and larger masses of **chromatin**, so called because it stains deeply with basic dyes. The largest clumps of chromatin
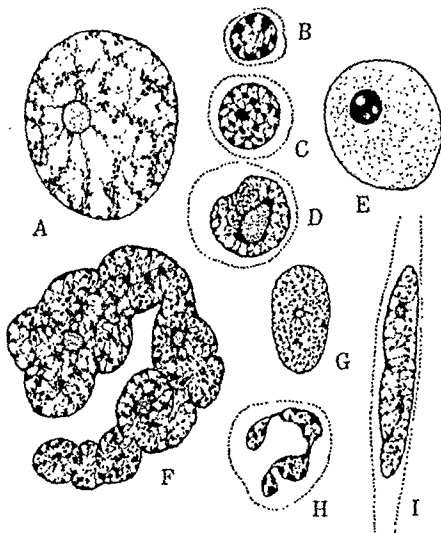
FIGURE 5. Variation in size, shape, and structure of nuclei: *A*, oocyte, *B*, lymphocyte, *C*, erythroblast from bone marrow; *D*, hemocytoblast from bone marrow; *E*, nerve cell of spinal cord, *F*, megakaryocyte of bone marrow, *G*, endothelium, *H*, neutrophil of blood, *I*, smooth muscle. 1800 ×.

are called **karyosomes**. During the interval between cell divisions, the nuclear boundary is marked by a prominently stained **nuclear membrane**. The nucleus usually contains one **nucleolus** which appears as an intensely staining, homogeneous, smooth, spherical body. The structure of nuclei is best illustrated in Figs. 4 and 5.

A relative amount of chromatin and its distribution pattern often serve

secretion or excretion take place. How these functions are carried out will be considered in biochemistry and general physiology. All cells possess them to some degree, although certain cells of multicellular organisms have specialized more for one function and others more for another. The cytoplasm is likewise the part of the cell that responds to stimuli, con-
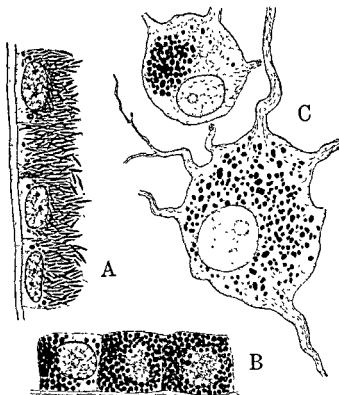

FIGURE 8. Cytoplasmic pigment· *A*, epithelium of rabbit retina; *B*, ciliary process of rabbit eye, *C*, autonomic nerve cells of monkey. Note the basement membranes in *A* and *B* 1200 ×

ducts impulses, and exhibits the phenomena of contraction and motility. The highest degree of specialization has been reached in respect to these functional activities of the cytoplasm. Just as there is a wider range of activity in the cell cytoplasm than in the nucleus, so there is a much greater variation of its structural pattern than that of the nucleus, where functions are more definitely limited.

Cytoplasmic inclusions are of various kinds. The cytoplasm of fixed and stained cells is usually granular, although it may present other appearances. One should first know whether the tissue was living or dead at the time of fixation and what and how fixing solutions were applied, in order to interpret cytoplasmic structure intelligently. The minute granules

ated sympathetic nerve cells are sometimes observed. Furthermore, the number of nuclei in a single skeletal muscle fiber (cell) commonly exceeds one hundred. Multinucleated elements may arise by nuclear division without cytoplasmic splitting. In other instances, fusion of a number of cells results in large multinucleated cells. Examples of multinucleated cells may be seen in Fig. 6. Watch for others in your slides.
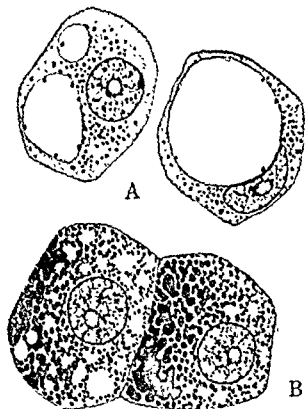

FIGURE 7. Cytoplasmic inclusions: A, liver cells of cat, showing spaces occupied in life by fat, and dark granules of bile pigment, B, liver cells of dog, filled with glycogen granules. 1200 ×.

Not only is the nucleus the most conspicuous component of the cell, but its functions are better known than those of other structures. It is the bearer of the **genes** that determine inherited characteristics. Note the precise manner of distribution of chromatin to the daughter cells during mitotic division (page 23). In the interval between divisions, the nucleus serves to preserve the chromosomes.

Without a nucleus, the cell is not only incapable of dividing, but its vitality is reduced because it cannot build up its protoplasm through constructive metabolism. The nonnucleated red blood corpuscles exist for a time and are then replaced. When a cell is cut in two, as in section of a nerve, the nonnucleated fragments invariably disintegrate promptly, because energy from protoplasmic substance is soon used up and the capacity for recovery and regeneration is lost. The nucleus regulates the metabolic activity of the cytoplasm. Just how it does this is unknown, but probably through some exchange of substances across the nuclear membrane.

Cytoplasm and its inclusions: The cytoplasm of the cell is the site of most cellular activities. Here cell respiration, assimilation of food material for energy metabolism, and synthesis of many special substances for

FIGURE 9. Centrosomes. A, oocyte, B, three embryonic epithelial cells (18-day chick), 1800 ×. C, living tumor cell showing conspicuous astral body (at arrow) and nucleus, both are encircled by fat droplets and granules, mitochondria are the filaments radiating from the central region Photomicrograph, 1100 ×, lent by Prof. Balduin Lucké.

cytize worn-out corpuscles contain pigments resulting from its decomposition.

Foreign particles may occasionally be observed in the cytoplasm of phagocytes. Common ones are coal, silica and other mineral dust (Fig.

are mainly coagulation artifacts. Coarser granules or vacuoles may represent **metabolic substances** that are taken in by the cell or are in process of elimination.

We can be quite certain about some of these cytoplasmic inclusions. For example, **glycogen** is demonstrable with appropriate technique. It is illustrated in Fig. 7B. Minute granules occur in practically all cells; larger amounts in liver, striated muscle, and certain specialized cells of heart muscle. **Fat** is commonly present in cells, but the usual technical procedures dissolve it and leave only spaces in the cytoplasm, as seen in Fig. 7A. Some cells, like those of adipose tissue and sebaceous glands, contain relatively large amounts. Others may become infiltrated with it during certain physiological states, notably the mammary gland cells during lactation. Other kinds of **lipoid droplets** may be encountered elsewhere in the body, *e.g.*, in cells of the suprarenal cortex. **Protein granules**, too, are present in consequence of cell metabolism.

How the various substances get into the cytoplasm of cells is not entirely known. Certain cells can engulf materials by processes of pinocytosis and phagocytosis, as you may see in motion pictures. However, it is probable that most food materials are brought in solution across the cell membrane from the interstitial fluid and that certain enzyme systems play important roles in this process.

Materials for secretion and excretion are made in the cytoplasm of cells, and evidence of their presence there may be seen in fixed and stained preparations. The **zymogen granules** in Fig. 29B represent secretion antecedents. Reference will be made to them in chapters dealing with glands.

Other **specific granules** of unknown function are prominent features of such cells as the granular leucocytes (Fig. 34). Nerve cells and some gland cells have flakes and particles of material that stain like nuclear chromatin with basic dyes. This has been called **chromophil substance** (Fig. 120A). The chromophil substance of nerve cells is called Nissl substance, for its discoverer. More will be said about it later.

Pigment appears as dark-brown granules or rods of melanin requiring no staining to be seen. Melanin pigment occurs in the epidermis of dark-skinned races, in hair, and in coats of the eye. It is illustrated in Fig. 8, which shows two kinds of cells. Its absence constitutes albinism. Other types of pigment may be found in the lutein cells of the ovary and in liver cells (Fig. 7A). Carotene colors epithelium yellowish. Hemoglobin imparts a greenish-yellow color to red blood corpuscles. Cells that phago-

astrocytes, have similar **glia** fibrils. We can only guess about the function of fibrils. Those of nerve cells are illustrated in Figs. 119 and 120.

As the electron microscope comes into greater use in cytology, it is to be expected that our horizon will broaden. A notable recent observation is the presence of extraordinarily minute **neurotubules** in nerve fibers. Their function is unknown.

Cell membrane: The boundary between cell cytoplasm and surrounding extracellular fluid constitutes a semipermeable **cell membrane** permitting the interchange between protoplasm and its environment, without which vital activities could not proceed. Do not overlook the importance of the cell membrane, even though you may have considerable difficulty in seeing it. It is usually not a real wall, and fortunately so, because walls would impede or limit the rapid transport from tissue fluid to intracellular fluid and vice versa. Many cells can increase and decrease the area of their surface membranes by extending or retracting protoplasmic processes in ameboid fashion. Occasionally, and perhaps transiently, intracellular canals provide increased surfaces (Fig. 29).

Where directional control is necessary, as on free surfaces in the intestines, sturdier, thicker borders are developed. **Striated borders** may be seen in Figs. 22 and 29A. They vary in thickness. **Brush borders** will be encountered in the kidney tubules. Substances secreted by cells form thick coatings for their free surfaces in a few places. The enamel of the developing tooth is such a **cuticle.** The greatest specialization at the cell surface is the ciliated border (Fig. 24). It may be actively motile, as in the cells lining respiratory passages.

FIGURE 10. Mitochondria as they appear with special staining in the intestinal epithelium of a chick embryo.

Shape of cells: It is principally variation in cytoplasmic organization that accounts for the wide variation in cell shape and size within the same individual. Typically, spherical cells are in the minority. Functional adaptation is responsible for many structural changes. Cells occurring in layers or masses tend to become polyhedral owing to mutual pressure. When
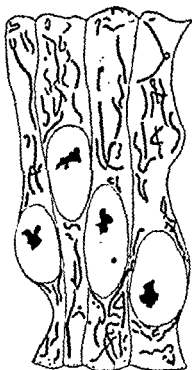
47), bacteria, spores of fungi; in fact, almost anything may show up in the cytoplasm of phagocytic cells.

Vacuoles of unknown significance appear in fixed and stained cells at times. One should always be skeptical of their interpretation and suspect faulty fixation, post-mortem artifacts, or early stages in cellular degeneration.

Cytoplasmic organoids: In contrast with the cytoplasmic inclusions, which vary widely in nature, amount, and distribution, certain other minute structures are found in almost all cells of the mammalian body. These are the organoids. Special techniques reveal them. You should not expect to see them in the usual preparations stained with hematoxylin and eosin. There is evidence that all of these exist in living cells in some form and that they have little-understood functions to perform in the cytoplasm.

Notable among the organoids is the **centrosome** (**diplosome**, if double), a tiny body in the **attraction sphere** that plays a part in cell division (page 26). That it likewise may be concerned in some way with certain intrinsic cytoplasmic movements, such as the movements of cilia and flagella, has been considered by some investigators. Figure 9 illustrates diplosomes in the cells of an embryo.

Mitochondria are found in all cells of animals but are less readily observed in fixed and stained cells than in fresh, supravitally stained tissues, because they are partly destroyed by lipoid solvents used in the usual technical procedures. Observe them in Fig. 9C. With adequate methods they appear as rods or filaments, as shown in Fig. 10. Their appearance varies with changing intracellular conditions. Mitochondria are distributed with remarkable regularity to the daughter cells during cell division. Although their function is unknown, a participation in secretory and absorptive processes of the cell has been suggested by some investigators.

The **internal reticular apparatus**, also called the Golgi network after its discoverer, is demonstrable only by silver impregnation techniques or after prolonged fixation with osmic acid solutions. Two characteristic appearances of it are demonstrated in Figs. 11A and B. A role in cell secretion has been suspected.

Other noteworthy organoids are fibrils, occurring with less regularity in cytoplasm of certain cells **Tonofibrils** have been encountered in some epithelial cells, **myofibrils**, in all muscle cells; and **neurofibrils** in all nerve cells. Fibroblasts of connective tissue are said to possess **fibroglia** fibrils under certain conditions. Somewhat comparable cells of the brain, the

odd forms, like the cells of tendons. Flattened plate-like cells most efficiently distribute their masses over wide surfaces, as in the closed body cavities and in blood vessels.

Cells that secrete tend to release their secretions through one region of the cytoplasm and acquire a fixed polarity. Cells which store fat and other materials and which are engaged in their own intrinsic function and have no call to move about and help regulate the activities of others most closely conform to the ideal spherical or eight- and fourteen-sided shapes. It is the active ones—the eager cells, as it were—that are thin, branched, and extended.

Cells of your body vary in size from about 4 μ in diameter to those visible to the naked eye. Some even attain a length of more than a meter. However, there is no correlation between body size and cell size. The cells of the giant are as small as those of the dwarf.

CELL GROWTH AND REPRODUCTION

Considerable space has been devoted to the description of the cytoplasm of cells, partly in hope that emphasis upon it will tend to counteract the tendency that many students have of thinking of blue-stained, clearly circumscribed nuclei in their preparations as the only important elements in cells. The nucleus is by no means the cell. In fact, it is only the director of the cellular activities. The real work of the cell is done by the constituents of the cytoplasm. These engage in contraction, secretion, and most of the other activities. Only when it comes to growth and reproduction does the nucleus come into its own. Even then, cytoplasmic constituents play important parts.

Growth of cells. Noncellular interstitial substances may increase in size by the addition of cellular secretions and water, but they do not grow in the true sense. Cells lacking nuclei may live a long time, but they do not grow. The nucleus is essential. Growth is a vital phenomenon involving the synthesis of proteins in the cytoplasm from materials assimilated by the cell and involving imbibition of water by these proteins.

Growth may be uniform in all directions, as in the human egg, or it may be confined to one or two poles and involve flowing-out of the protoplasm, as in nerve-cell processes. Increase in cell size can result from the combining of two or more small cells to make one big one, like the giant, multinucleated, phagocytic, "foreign body" cell. There is a limit beyond which a cell can no longer increase in size.

spheres are arranged in a single layer, each borders upon six neighbors and thus becomes a polyhedron with eight sides. Superimposition of layer upon layer leads to formation of fourteen-sided polyhedrons (tetrakaidecahedrons), conforming to an ideal geometrical design which encloses the
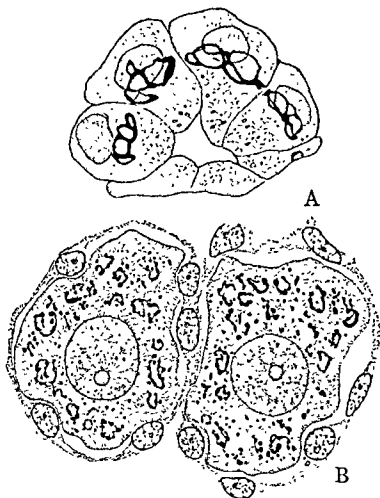

FIGURE 11. Internal reticular apparatus (Golgi): *A*, salivary gland cells, silver stain, *B*, spinal ganglion cells, osmic acid stain. 1200 ×.

greatest mass with the least surface. Few actually conform to this ideal, notably the cells of multilayered epithelia and those of adipose tissue.

Almost every conceivable shape is encountered in the body. Elongation is a modification favoring contractility and conductivity, as seen in muscle and nerve cells. Stellate forms occur in response to the need for increased surface, as in nerve cells, inactive macrophages, and fibroblasts. Pressure of other cells or of intercellular structures produces

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Cell division is essential for growth of the whole organism. Protoplasm functions best in small units, but cell division cannot go on indefinitely without cell growth. The fertilized egg, a very big cell to begin with, divides and redivides until a multicellular blastocyst has been formed which is scarcely bigger than the original egg but whose individual cells are much smaller. Some of the body cells, such as lymphocytes, grow large and then divide into two daughter cells of ordinary mean size. In most instances, however, cells of mean size divide into smaller daughter cells, which then grow quickly to mean size.

Reproduction of cells: The cell division that has to do with propagating the species is vested in special cells of the gonads. That which is concerned with growth and maintenance is more widely exhibited. Stages in cell division are encountered more frequently in tissues of young individuals or fetuses than in adults. They are numerous in rampant neoplastic growth. The process of cell reproduction slows down in normal tissues with advancing age. Indeed, after maturity has been reached,
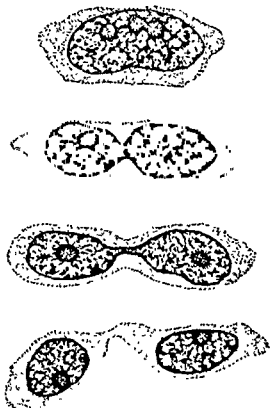
FIGURE 12. Amitotic cell division suggested by a selected series of cells of the urinary bladder epithelium 1200 ×.

all cell divisions except those in the gonads are for the purpose of replacement or repair.

Frequency of cell division in an organ depends largely upon the life span of its component cells, and it varies widely. Nerve cells, for instance, live as long as the individual and are not replaced if destroyed. Cell divisions are not encountered in the nerve cells. On the other hand, we find such cells as red and white blood corpuscles with short lives. They are elements that have to be replaced continuously. Cell division never ceases in the organs that produce them.

The definitive cells of the body, formed by cell divisions, do not themselves divide. A whole different category of cells is that whose members

live a while, divide to produce a definitive cell and another reproducer, and go on and on in this way throughout life. In other words, these are
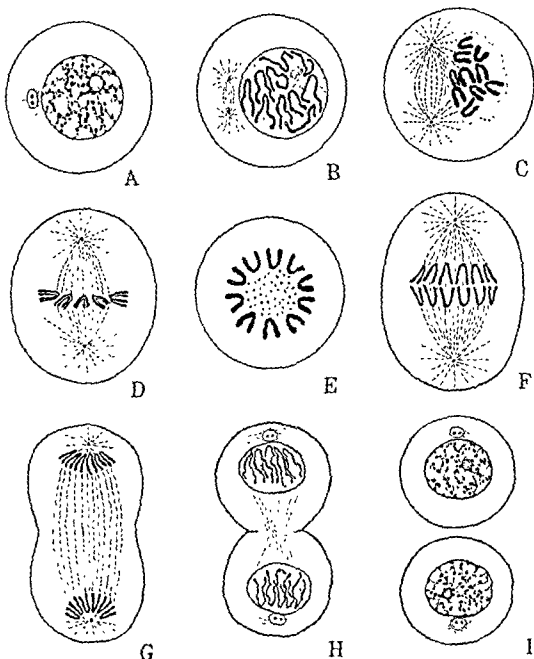

FIGURE 13. Diagram of mitotic cell division in an animal cell A, B, and C, prophase, D and E, lateral and polar views of metaphase, F and G, anaphase, H and I, telophase.

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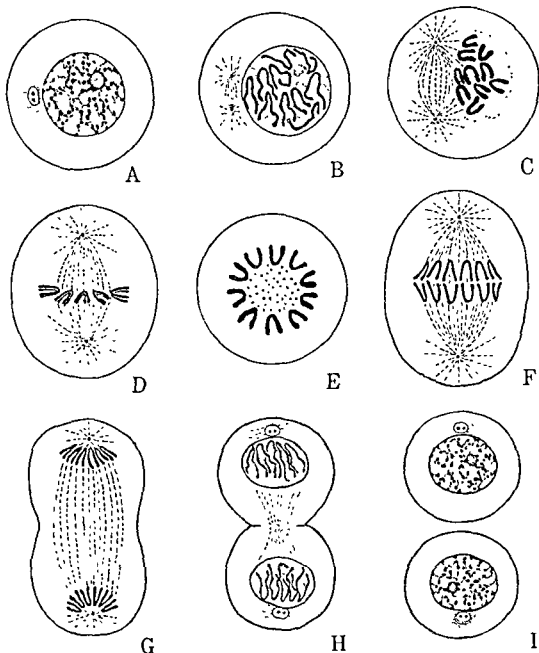

FIGURE 13 Diagram of mitotic cell division in an animal cell. A, B, and C, prophase; D and E, lateral and polar views of metaphase, F and G, anaphase, H and I, telophase.

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Reproduction of cells: The cell division that has to do with propagating the species is vested in special cells of the gonads. That which is concerned with growth and maintenance is more widely exhibited. *Stages in cell division are encountered more frequently in tissues of young individuals or fetuses than in adults.* They are numerous in rampant neoplastic growth. The process of cell reproduction slows down in normal tissues with advancin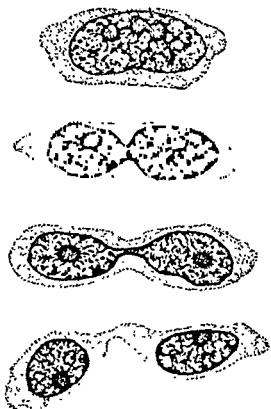g age. Indeed, after maturity has been reached, all cell divisions except those in the gonads are for the purpose of replacement or repair.

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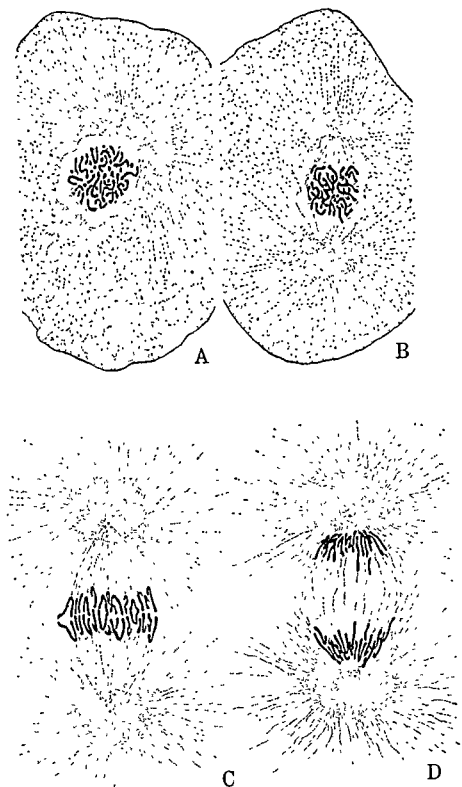
FIGURE 15 Mitosis in fertilized eggs of the whitefish. *A*, prophase; *B*, metaphase; *C* and *D*, anaphase 1200 ×.

the nucleus and cytoplasm by the process known as **amitosis**. Or it may be, and usually is, a much more complicated, indirect division, to which the name **mitosis** is applied. There is reason to believe that amitosis comes about primarily, if not entirely, in cells whose metabolism is impaired in some way or in cells that are on the verge of death. Figure 12 illustrates several stages in the process seen in the bladder epithelium.
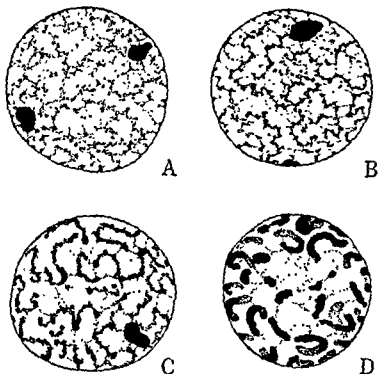

FIGURE 14 Four stages in the prophase of oögonial nuclei (pig embryo) to show condensation of diffuse chromatin into chromosomes. 1800 ×.

Mitosis is the process of reproduction of healthy active cells. Its outstanding feature is a temporary disappearance of the nucleus following condensation of the chromatin into filaments, called **chromosomes**. These undergo an even longitudinal splitting, and the halves are divided between the daughter cells. The term mitosis refers to the chromosomes; it means thread. It is customary to give names to the principal phases of the process of condensation, splitting, and pulling apart of the chromosomes in mitosis. These phases are illustrated diagrammatically in Fig. 13.

The **prophase** is concerned with formation of the chromosomes. Chromatin is scattered along the linin network of the resting nucleus. The threads of this network gradually shorten. The granules of chromatin are pulled together and stain more darkly. Thus, twisted filaments, called

Fig. 15A. The two centrosomes move away from each other, carrying along halves of the attraction sphere and rays (Figs. 13B and C). Some of the rays of each of the resulting **amphiasters** become attached to each of the chromosomes. Amphiasters at the two poles of the cells are connected by means of **mantle fibers,** in the center of which are the chromosomes at the end of the prophase.
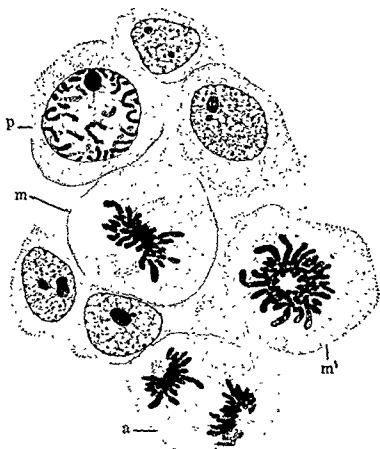

FIGURE 17. Group of cells in the ovary of a pig embryo: *a,* anaphase, *m* and *m',* lateral and polar views of metaphase, *p,* prophase. 1200 ×.

The number of chromosomes is constant for all body cells of each species. There are 48 in man.

Chromosomes are of various sizes and various shapes, like those seen in Fig 15C. They occur in pairs. Each one of a given shape and size has a mate with identical characteristics. In other words, the nucleus actually contains a series of mated **homologous chromosomes,** one member of each pair derived from the paternal and the other from the maternal parent. Species with an odd number of chromosomes possess one extra,

spireme threads, are formed. These changes are shown in Figs. 14A, B, and C. The chromatin is condensed further, and the spireme breaks up into chromosomes (Fig. 14D) as the connecting linin network and nu-
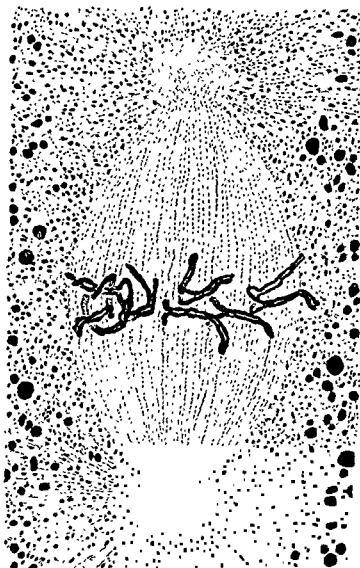

FIGURE 16. Metaphase in fertilized egg of the frog, to show chromosome splitting. Small granules are pigment; large granules, yolk 2400 ×.

clear membrane disappear. The chromosomes, lying free in the cytoplasm, may exhibit thin longitudinal clefts, indicative of the plane of separation to be effected in the next stage.

Coincident with nuclear changes, the centrosome, which is already double, becomes prominent, and its attraction sphere sends rays out in the cytoplasm, forming a star-shaped body, the **aster**, like that illustrated in

Fig. 15A. The two centrosomes move away from each other, carrying along halves of the attraction sphere and rays (Figs. 13B and C). Some of the rays of each of the resulting **amphiasters** become attached to each of the chromosomes. Amphiasters at the two poles of the cells are connected by means of **mantle fibers**, in the center of which are the chromosomes at the end of the prophase.
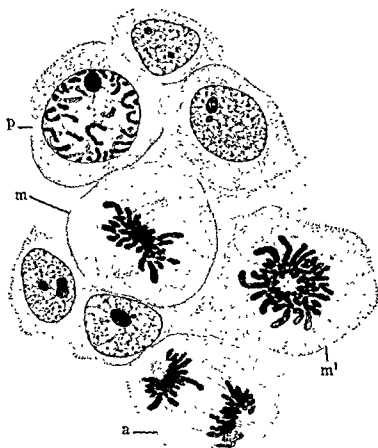

FIGURE 17 Group of cells in the ovary of a pig embryo. *a*, anaphase, *m* and *m'*, lateral and polar views of metaphase, *p*, prophase 1200 ×

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which is the **sex chromosome**. Man, with an even number of chromosomes, has a pair of sex chromosomes.

The **metaphase** is the stage during which the splitting chromosomes are arranged at the equator of the cell in readiness to be drawn apart. They appear as if suspended by threads, the mantle fibers, in a single plane midway between the two asters. This is illustrated diagrammatically in Fig. 13D. When viewed from one pole of the cell, chromosomes appear as in Fig. 13E. More realistic pictures are those in Figs. 16 and 17.

The **anaphase** sees the complete separation of halves of each chromosome and their migration to opposite poles of the central spindle. In diagram, this is shown in Figs. 13F and G; better in Figs. 15C and D and 17. Separation of the chromosomes begins at points of attachment of the mantle fibers. As the separating chromosomes move apart, there are fine lines left behind them connecting one with another. The number of chromosomes at either pole of the cell at the end of the anaphase is exactly the same as the number in the cell at the prophase. It is the number characteristic of the species.

The **telophase** is the reverse of the prophase. The compact chromosomes grow in length and are soon found to be connected with one another by the linin network (Fig. 13H). The nuclear membrane is reformed. Aster fibrils fade from view gradually. The centrosomes divide in preparation for the next mitotic division (Fig. 13I). The cell cytoplasm constricts between the daughter nuclei, and two new cells have been formed in place of one.

The time required for completion of one cell division varies with the type of tissue and the species. In some, it is an hour or less; two or three hours is common. In tissue cultures of fibroblast cells, the prophase takes thirty to sixty minutes. The chromosomes remain in the equatorial plate at the metaphase for a time varying from only a minute or two to fifteen minutes or more. The actual migration takes only two or three minutes. Thus the anaphase is brief. The telophase, from the arrival of chromosomes at the poles until the separation of the daughter cells, takes three to six minutes. The period of rest and growth varies between one-half hour and two hours in these tissue culture cells. From a consideration of these facts, it appears that the greatest number of mitotic figures that will be encountered will be prophases. The actual pulling apart of the chromosomes is rarely encountered. The relative times for each of these phases can be observed very nicely in a motion picture.[1]

[1] See Visual Aids 1, 2, and 8.

Mitotic cell divisions take place in most tissues of the adult body. An unusual type occurs during maturation of the germ cells in the ovary and testis. This involves no splitting of the chromosomes, but a division of the homologous chromosomes. This process, in which there is a reduction to half of the species number of chromosomes, is called **meiosis**.

AGING AND DEGENERATION OF CELLS

Although we are so accustomed to thinking of cells as the living components of tissues that we have so designated them in the heading of the present chapter, we must not overlook the fact that some normal healthy tissues of the body are composed, in very significant part, of cells that are in the process of dying or are actually dead. We are not concerned with the cells that die rapidly as a result of disease processes. That is a subject for the pathologist. We are called upon to take into account the gradual degeneration and death due to aging of cells and especially to slow degenerative changes that ultimately benefit the organ as a whole. Such changes constitute **physiological degeneration**.

Aging is a phenomenon of great importance to all. Its study is known as geriatrics. We are no sooner born than we begin to grow old. Some of our organs start to degenerate before birth. One of the most notable examples of this is the change that takes place in some of the blood vessels which were of great functional value before birth but which are undesirable after birth. The umbilical arteries and the ductus arteriosus are examples.

The scope of your course in histology is not broad enough to encompass the entire range of structural pictures of tissues and organs from the time of birth until senility, which form a basis for adequate understanding of the phenomenon of aging. However, from time to time outstanding age differences will be discussed. It is hoped that you will avoid fixed concepts of the structure of various organs. The histology of the child and that of the aged are significantly different from the picture usually presented as representative of any particular organ.

Physiological degeneration of cells begins before birth and extends throughout life. A few examples will be considered. The barrier between the external environment and the body protoplasm is the surface of the skin. Stages in transformation of living epithelial cells to dead scale-like cornified cells that protect the body against the external environment are demonstrated in Fig. 18B. The cornified cells are constantly sloughed off

the surface of the body by a process known as desquamation. They are replaced by other cells formed mitotically, as will be seen in studying the skin (page 244). Physiological degeneration of cells of sebaceous glands
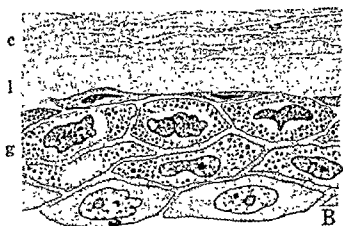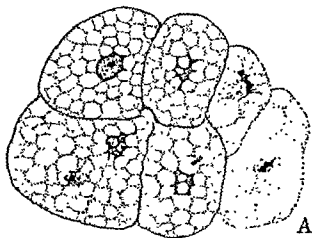

FIGURE 18. *Physiological degeneration of cells: A, sebaceous gland, B, cornified stratified squamous epithelium, c, stratum corneum; g, stratum granulosum; l, stratum lucidum.* 1200 ×.

for the purpose of producing a material to lubricate the surface of the body is illustrated in Fig. 18A. Another example of physiological degeneration is the loss of nuclei from cells of the bone marrow to produce red blood corpuscles. In this way are produced the little hemoglobin-filled plastids which, without nuclei, are able to lead fast and strenuous lives.

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Epithelium

Epithelium covers surfaces and lines cavities for the most part. It is the only tissue you see when you view yourself or others. Hair, nails, the outer layer of skin, the front of the eyeballs, the nasal and oral linings are made of epithelial cells. In fact, all you ordinarily see of any healthy living thing is epithelium. You can readily verify this by scraping off a few surface cells—your own skin is most convenient—and studying them in a drop of water under the microscope.

CHARACTERISTICS OF EPITHELIUM

Epithelium is the most cellular tissue of the body. The cells are always placed in close proximity to one another, like bricks in a wall. And, like bricks, they are cemented together with a matrix material. Epithelium fits into the concept of tissues composed of cells, interstitial fluid, and matrix substance, but with the greatest emphasis on its cells.

The **intercellular cement** or matrix substance is not solidified. It is a semifluid material occurring in such small amounts that it cannot be seen in histological sections with the usual staining procedures. It can be brought out after immersing fresh epithelium in weak solutions of silver nitrate and subsequently exposing them to sunlight. Precipitation of silver salts causes the intercellular substance to appear dark brown or black (Fig. 19). Scanty as it is, this substance provides the cells some direct contact with the interstitial fluid. By diffusion, oxygen and other dissolved substances can reach its cells through the intercellular cement.

The cells of the outer surface of your body are not living but have undergone physiological degeneration to provide an armor against the external environment. They are dry, in contrast to the moist living cells of

respiratory and digestive passages, which are constantly bathed in body secretions or fluids taken in periodically by mouth.

Epithelial cells are not always exactly alike but vary according to their location and function. They may occur in a single layer as simple epithelium or be piled layer upon layer to constitute stratified epithelium.

Protection is not the only function of epithelium. Some epithelial cells are specialized to facilitate rapid passage of fluids through them. Some have secretory functions. Others have developed special characteristics, permitting reception of messages from the external or internal environment to initiate nerve impulses. Sometimes several functions are served by different cells of a single epithelial layer, e.g., neuroepithelial cells in a layer of protective epithelium.

Epithelium presents one **free surface** to the outer environment. This may be composed of dead cornified elements, as in the outer layer of the skin, or thickened cell surfaces, such as the striated border of cells in the digestive tract. The surface may be specialized in other ways; the ciliated free surface of cells in the respiratory tract is an example.

Its **basal surface** is presented to the internal environment and may be more or less sharply defined according to the development of a **basement membrane** separating it in most places from underlying connective tissue (Fig. 20C). This basement membrane is sometimes lacking, for example, in the thyroid and urinary bladder. In its least well-developed state, it consists of an indistinct layer of delicate fibrils. When better developed, it is a definite lamina of connective-tissue fibers, and even cells, and it presents a homogeneous appearance (Fig. 20).

Through the basal surface of epithelium, substances needed for vital functions of its component cells must pass. With minor exceptions, epithelia, even when highly stratified, have no blood vessels in them and must depend upon diffusion through interstitial fluid. Not only do fluids pass among the cells of epithelia; white blood corpuscles may be found, often in great numbers, making their way through the intercellular substance (Figs. 24 and 193). Fine nerve terminations also occur among epithelial cells (Fig. 138A).

Thus, we learn that the bricks in our wall are not too tightly cemented together. When the wall has been broken, they can actually move and extend processes to help close the gap. Simple, uncomplicated wounds in stratified epithelium are healed in this way. The gliding of cell upon cell in the epithelium of the urinary bladder is noteworthy in considering movements of epithelial cells. Such structures as **intercellular bridges**

and **terminal bars,** seen in Figs. 22 and 27, play some part in holding
components of epithelium together. They are not encountered in those
layers which exhibit movement of cells over one another.

TYPES OF EPITHELIUM

It is customary to classify epithelia into **simple** and **stratified,** accord-
ing to whether they consist of one or more layers. It is also customary to
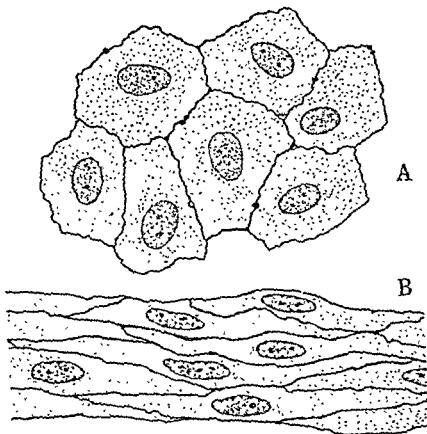

FIGURE 19 Simple squamous epithelium: A, mesothelium on the
surface of guinea pig mesentery, B, endothelium lining a small vein
of the same Intercellular cement is darkened by silver. 1200 ×.

. . . . component cells. The outermost
. . . . ame. Flat cells impart the name
squamous, and tall cells, **columnar.** Columnar epithelium may be pro-
vided with cilia on the free surface to complicate its classification further.
You will find **simple squamous** and **simple columnar** epithelia, also
stratified squamous and **stratified columnar.** Furthermore, there are two
special categories. A variety of simple columnar epithelium has low,

medium-high, and tall cells. All rest on the basement membrane, but only the tall cells reach the surface. This is called **pseudostratified** epithelium.

A variety of stratified epithelium occurring only in the urinary tract, notably the bladder, is designated **transitional** epithelium. Its superficial cells are irregular in shape but have considerable height and so should be
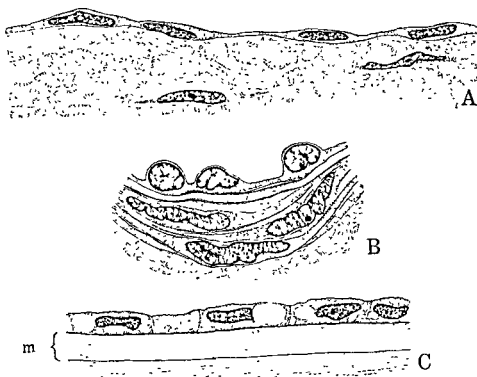

FIGURE 20 Simple squamous epithelium. A, flat mesothelium on fibrous connective tissue of the serous coat of the monkey gall bladder, B, bulging nuclei in endothelium of a contracted arteriole from the same animal, C, thick simple squamous epithelium with a prominent basement membrane, m, on the posterior surface of a rabbit's cornea 1200 ×.

classed as columnar During distention of the urinary bladder, they become quite flat, and the number of layers decreases as the cells slide past one another to adjust to the increased surface area.

Simple squamous· Sheets of flat cells, bulging at their nuclei and joined to one another with intercellular cement substance, make up simple squamous epithelium. Figure 19 illustrates this type in surface view. Resemblance to a platter of fried eggs is often suggested. Some simple squamous epithelia are thinner than others (Figs. 20A, B, and C).

Simple squamous epithelium is never found in exposed places where protection is needed, nor does it occur where absorption or secretion is the requirement. It is the epithelium of the blood-tissue fluid barrier and

the tissue fluid-lymph barrier. In other words, it occurs where thin semi-permeable membranes must be set up between two fluids. It occurs also in places where a simple compartmentalizing tissue is needed.

Under the name **endothelium**, it forms linings of capillaries, then continues into the larger blood vessels and the heart (Figs. 19*B* and 20*A* and *B*). It is so very thin in some places, *e.g.*, in the bone marrow sinusoids, that we cannot be certain it forms a complete barrier.
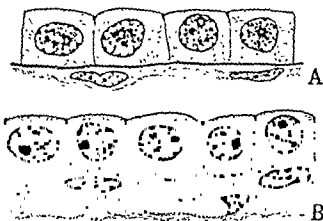

FIGURE 21. Low simple columnar epithelium: *A*, small renal collecting tubule of a monkey; *B*, thyroid follicle of a monkey. Terminal bars are shown as black patches at cell junctions. 1200 ×.

Simple squamous epithelium lines the body compartments, where it goes by the name **mesothelium** in peritoneal, pleural, and pericardial cavities (Fig. 19*A*). Similarly, it lines the spaces containing other special tissue fluids, like the aqueous humor of the eye (Fig. 20*C*), fluids of the internal ear, and cerebrospinal fluid.

In the lung alveoli, simple squamous epithelium is said to form an exquisitely thin lining, although some dispute this. On one side of this lining is tissue fluid; on the other, the thin film of fluid coating the respiratory tract. It is encountered on a few other moist surfaces. It will be found in some very small excretory tubules.

Simple columnar: Thicker cells form **simple columnar epithelium**. The facets by which each cell joins its neighbors may be as great or greater in area than the outer and inner cell surfaces. This type of epithelium is illustrated in Figs. 21 and 22. Simple columnar epithelium has greater protective qualities than simple squamous epithelium, but protection is not its principal function. If we include its special pseudostratified variant, we can say it is the only type of epithelium concerned with secretion

and absorption. It is one of the main epithelia lining excretory passages. Most other functions are incidental specializations.

In simple columnar epithelium, the outer border of the cells is apt to be specialized. **Brush borders** (Fig. 9) and **striated borders** (Figs. 22 and 29A) are associated with the phenomenon of absorption. The highest degree of specialization is seen in the formation of **cilia** (Figs. 23 and 24).
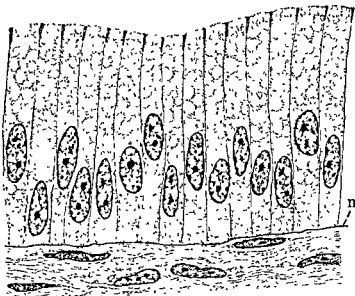

FIGURE 22. Tall simple columnar epithelium lining the monkey gall bladder Prominent terminal bars and faintly striated border are present; a delicate basement membrane, *m*, is seen above connective tissue. 1200 ×.

Cilia are not always motile (Fig. 25), but when they are, they move secretions or excretions along the surface.

Low simple columnar epithelium, called cuboidal by some, presents its most characteristic appearance in glands and gland-like organs It will be found in the thyroid, in tubules of the kidney, and in the pigmented layer of the retina. These examples are illustrated in Figs. 8A and B and 21. In modified form, low columnar epithelium occurs in the liver In most of the endocrine glands, cells resembling low columnar epithelium occur in cords and masses, rather than in sheets or layers. Perhaps they should be indicated by the name **epithelioid cells** (Fig. 31D).

High simple columnar epithelium is least specialized in the gall bladder (Fig. 22). It lines the intestines, where absorptive cells alternate with mucus-secreting elements, as shown in Fig. 29A. It is found also in glands (Figs. 31 and 32) and in many glandular ducts, where its cells assume the shape of truncated pyramids. The simple columnar epithelia of the

uterus, uterine tube, and small bronchi possess active cilia. Ciliated cells often alternate with secreting cells of simple columnar epithelium, as shown in Fig. 23.

Pseudostratified: The type of epithelium illustrated in Figs. 24 and 25 is called **pseudostratified**. It occurs throughout most of the respiratory tract and in the male genital passages. Active cilia are present on most of the respiratory ep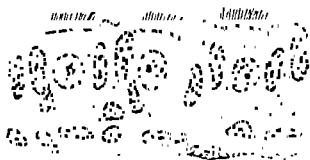ithelial cells. Inactive cilia are said to be present in the male reproductive tubes. Mucus-secreting cells alternate with ciliated excretory cells in the epithelium of the respiratory passages (Fig. 24). Nonciliated pseudostratified epithelium is rare. It is found only in a few large excretory ducts.

FIGURE 23. Simple columnar epithelium of cat's uterine tube. Ciliated cells alternate with groups of nonciliated cells. 1200 ×.

Stratified columnar: Like nonciliated pseudostratified epithelium, the truly **stratified columnar epithelium** is of rare occurrence and need not concern you greatly. It may be encountered in a few large excretory ducts.

Stratified squamous: The esophagus is lined with typical **stratified squamous epithelium.** Figure 26 shows it in that organ. The cells of the lowest or basal layer are tall. The outside layers are flat, and they are the ones that give the name squamous to the epithelium. Cells of the intervening layers vary in height as they are pushed upward toward the flattened surface. They are firmly attached to one another. You can sometimes observe intercellular protoplasmic bridges like those shown in Fig. 27.

Epithelium similar to this—and likewise basally indented by connective tissue—occurs in the mouth, oral pharynx, upper part of the larynx, lower part of the anus, the vagina, and outer part of the urethra. In fact, it is found wherever a combination of moist surface and high degree of protection from abrasion is required. A simpler type covers the transparent cornea of the eye (Fig. 152). Glands are associated with stratified squamous epithelium in these locations to provide lubricating fluid. It is noteworthy that other types of epithelium, when subjected to exposure, drying, and abrasion, can become stratified squamous epithelium The process by which they are transformed is called metaplasia.

Stratified squamous epithelium of the **cornified** variety, illustrated in Figs. 170 and 171, covers the entire external surface of the body, giving way to the noncornified type at all the body orifices. With its appendages, the hair, nails, and sweat and sebaceous glands, it presents special features which can best be considered in the chapter on the integument (page 244).

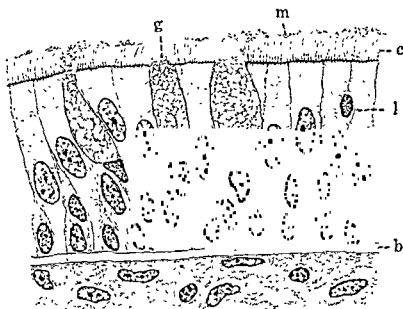*Transitional:* Structurally and functionally similar to stratified squamous

FIGURE 24. Pseudostratified epithelium with motile cilia, *c*, lining monkey trachea Goblet cells, *g*, are pouring mucus, *m*, onto the epithelial surface; a prominent basement membrane, *b*, is present above loose connective tissue; a lymphocyte, *l*, is migrating through the epithelium. 1200 ×

epithelium is **transitional epithelium.** One difference is that its cells are freer to move over one another. They do so in the urinary bladder as that organ fills and empties. This change is shown in Fig. 28. In transitional and in other stratified epithelia, growth and replacement of cells take place in the basal layer. Stages of mitosis are ordinarily found there and at higher layers. Direct cell divisions may occur in the superficial layers of the bladder epithelium (Fig. 12).

GLANDULAR EPITHELIUM AND GLANDS

Many cells of simple columnar and some of those of other types of epithelium are concerned with the phenomenon of secretion. All living

cells give off products of their metabolic activities. Most of these are of no use to the organism as a whole and constitute waste products that must be excreted elsewhere in the body. Some cells manufacture substances not for their own use nor as a by-product of their own metabolism. Their products are called secretions, whether extruded into a duct or diffused through endothelium of adjacent capillaries into the blood stream.
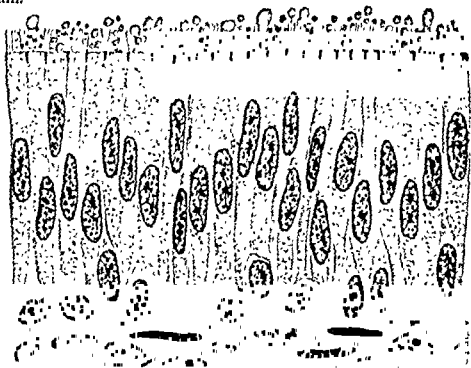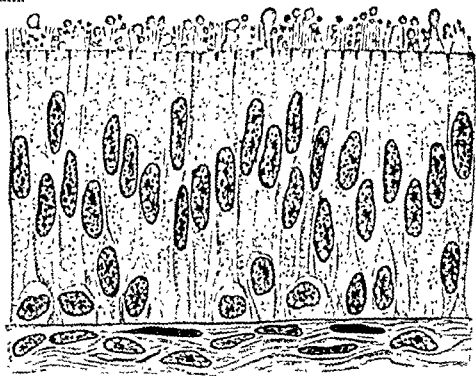

FIGURE 25 Pseudostratified epithelium, actively secretory, showing surface projections which appear to be nonmotile cilia but which may be extensions of the intercellular projections of matrix covered with secretion. Specimen is from the epididymis of a ram, 1200 ×.

Groups of cells engaged in secretion into ducts form the common **exocrine glands** like the salivary glands. Groups whose secretions pass into the tissue fluid and enter the blood stream are ductless and constitute the **endocrine glands,** or glands of internal secretions. The thyroid is a good example.

The epithelial cells of exocrine glands exhibit a polarity. The antecedents of their secretions first appear as minute droplets or granules in the basal half of the cell where the nucleus is usually located. The droplets increase in size and move toward the free surface of the cell where they may accumulate as masses of round granules or where they may run together into larger drops.

In most glandular epithelium, watery secretions diffuse through the free surface membrane of the cell without producing visible change in
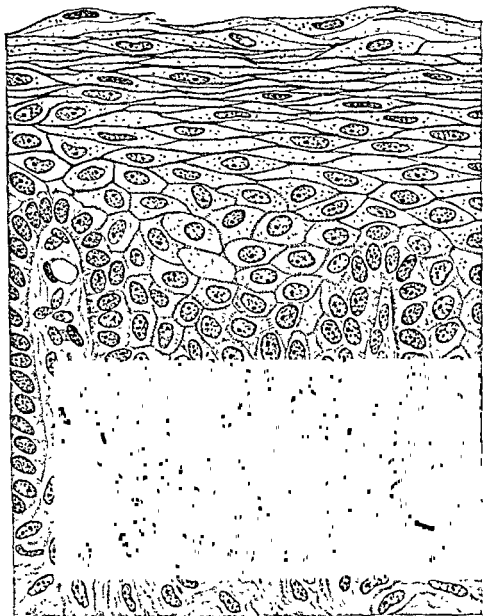
FIGURE 26. Stratified squamous epithelium lining the esophagus of a 1-year-old human infant. Papillae of connective tissue indent the epithelium. Note that the magnification is less than other illustrations of epithelia. 900 ×.

it. Glands secreting in this manner are classified as **merocrine glands,** cells of which are illustrated in Figs. 29B and C.

In other cells, the secretion cannot be released unless the cell membrane on the free surface is altered. Often it appears to be dissolved, and

cells give off products of their metabolic activities. Most of these are of no use to the organism as a whole and constitute waste products that must be excreted elsewhere in the body. Some cells manufacture substances not for their own use nor as a by-product of their own metabolism. Their products are called secretions, whether extruded into a duct or diffused through endothelium of adjacent capillaries into the blood stream.

FIGURE 25 Pseudostratified epithelium, actively secretory, showing surface projections which appear to be nonmotile cilia but which may be extensions of the intercellular projections of matrix covered with secretion. Specimen is from the epididymis of a ram. 1200 ×.

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such as uterine and intestinal glands (Fig. 31A), or they may be long coiled tubes like those of the sweat glands (Figs. 167 and 176). In some
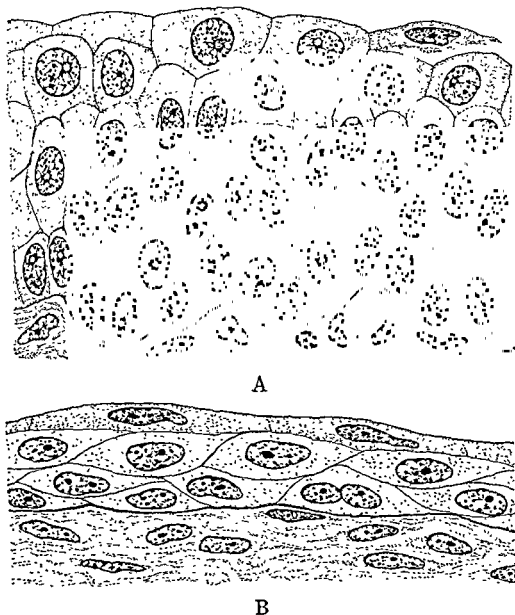

A

B

FIGURE 28. Transitional epithelium. A, contracted urinary bladder of a dog; B, distended urinary bladder of a rabbit. 1200 ×.

locations, several tubular glands open into one duct, forming a branched tubular gland (Fig. 31B).

The next step in increasing glandular complexity is produced by lateral outpocketing from the simple tubule, which thus becomes branched (Fig. 31C). The blind ends of the branches may be dilated, and secretory cells

a small portion of the cytoplasm beneath it undergoes destruction. Such a process, illustrated in Fig. 30, occurs in **apocrine glands.**

Cells of a few glands produce lipoid secretions and die in the process. The sebaceous glands are of this **holocrine** type. They are formed by stratified squamous epithelium. Their degenerating, secretion-filled cells are replaced as rapidly as they are destroyed. A detail of their structure is represented in Fig. 18.
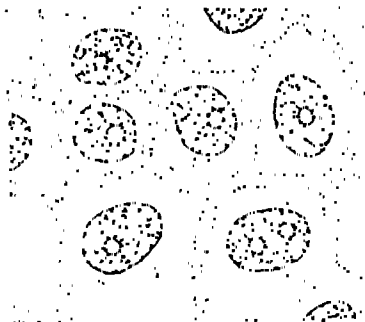
FIGURE 27. Intercellular bridges between cells of stratum germinativum of cat's paw epithelium. 1800 ×.

Secretory cells scattered among nonsecretory cells of simple columnar and pseudostratified epithelium may be regarded as **unicellular glands.** Typical of these are the mucus-secreting cells of intestinal and tracheal epithelium, called **goblet cells** because of their shape (Figs. 24 and 29A). Mucus at first appears as minute droplets which run together and cause a swelling in the cytoplasm of the cell, deforming the basally placed nucleus and compressing adjacent cells. The mucus is usually discharged as a single mass, leaving the unicellular gland thin and exhausted.

Multicellular glands are formed of epithelial cells arranged in various ways for the purpose of increasing the secretory surface. Some glands are of microscopic size, like the tiny ones in walls of the mouth, trachea, stomach, and intestines. Others are so large that they may weigh hundreds of grams. The liver is in the latter category. Multicellular glands may be simple **tubules—**relatively short depressions of an epithelium—

face of epithelium. Their secretions traverse a system of ducts and are poured out onto the epithelial surface. The complexity of the duct system is related to the size of the gland. In the largest glands, secretion is carried considerable distances, and the glands may be placed far away from the epithelium onto which it is emptied.

FIGURE 30. Secretory phenomena in simple columnar cells of human uterine gland. Preparation by Dr. G. N. Papanicolaou. 1200 ×.

The large glands are subdivided into lobes and lobules and are elaborately supplied with blood vessels, lymphatic vessels, and nerves.

Endocrine glands may arise embryologically as simple outpocketings from epithelium, but they lose this connection and most of them present the appearance shown in Fig. 31D. Occasionally a remnant of the duct may persist, such as the thyroglossal duct of the thyroid gland.

Cells of exocrine glands are not always of one type. Some acinous and tubulo-acinous glands have two varieties of cells: **serous** and **mucous**. These may be intermingled in one acinus or may occupy different acini. The submandibular salivary gland is an example of one with components producing both watery, serous fluid and thicker mucus. In sections stained with hematoxylin and eosin, serous cells are apt to be unstained or stained pink, and mucous cells, blue. Some mucous cells look pale, and some serous cells contain blue chromophil substance. There are always exceptions to plague you. Serous cells have elliptical nuclei, whereas the

may be confined to these dilations. The thinner tubular portions become the ducts, and the dilations are called **acini** or **alveoli**. A gland constructed in this manner is called an acinous or alveolar gland. Several
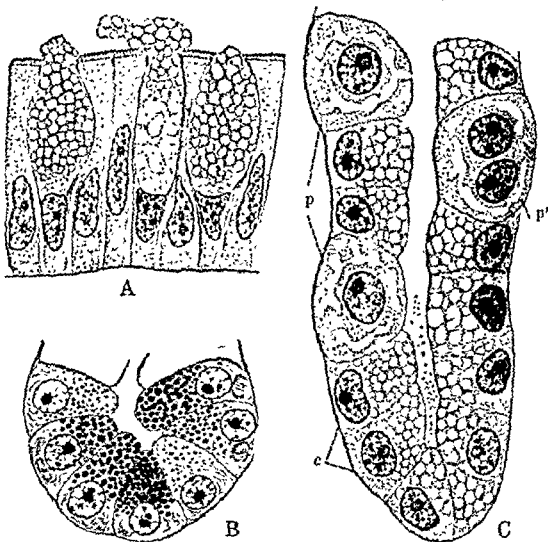

FIGURE 29. Glandular epithelium. A, goblet cells, secreting mucus, among absorptive cells with striated borders, in the small intestine of a cat; B, zymogen granules in cells of a pancreatic acinus of a kitten, C, termination of a principal gland of a monkey's stomach, showing pepsin-secreting chief cells, c, and acid-producing parietal cells, p Note the intracellular secretory canaliculae, p'. 1200 ×.

acini opening along the course of one duct or forming a cluster at the end of a duct build a simple branched acinous gland. Such a gland resembles a bunch of grapes, with the main duct representing the stem. Glands that combine the structure of tubular and acinous glands are called **tubulo-acinous**. They are compound glands The parotid is an example.

Large exocrine glands are located in connective tissue beneath the sur-

Furthermore, some of the endocrine glands have several types of cells. Finally, glands will be studied that are made up of both exocrine and endocrine elements. An example is the pancreas. Each of the examples mentioned here will be considered further in later chapters.
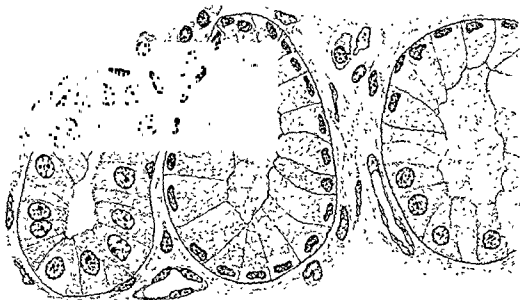

FIGURE 32. Serous (left), mucous (middle), and mixed (right) acini of a human tracheal gland. 900 ×.

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      Wounds of the Cornea, *Anatomical Record*, vol. 86, pp. 75–86, 1943.
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      read this A more complete treatise on the subject of epithelial wounds will
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2. Maximow, A. A., and W Bloom· Epithelium, being Chap. 2, pp. 26–39,
      and Glands, being Chap 13, pp. 288–296, in *A Textbook of Histology*,
      5th ed ; Philadelphia, W. B. Saunders Company, 1948.
      *Here you will find a considerable amount of additional information on the
      subjects covered in this chapter. Other references to articles on epithelium
      and glands are provided.*

mucous-cell nuclei are usually flattened and pressed against the base of the cell. These differences are illustrated in Fig. 32. Crescentic groups of serous cells are often seen pushed aside by swollen mucous cells, form-
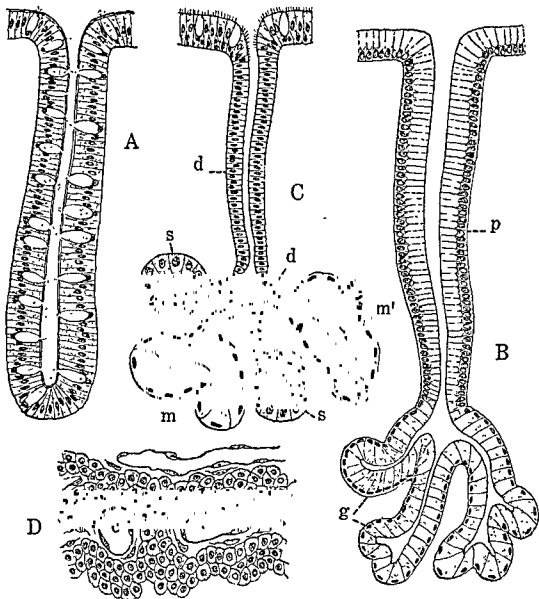
FIGURE 31. Diagram of glands of several types: A, simple tubular intestinal gland, B, branched tubular pyloric glands; C, tubulo-acinous gland with serous, s, mucous, m, and mixed serous and mucous, m', acini and ducts, d; D, endocrine epithelioid-cell cords with blood capillaries, c.

ing caps for mucous acini. These are called demilunes in the submandibular and sublingual salivary glands (Fig 191).

Mixed tubular glands will be found. The glands encountered in the stomach walls have cells of three types, two of which are seen in Fig. 29C.

Furthermore, some of the endocrine glands have several types of cells. Finally, glands will be studied that are made up of both exocrine and endocrine elements. An example is the pancreas. Each of the examples mentioned here will be considered further in later chapters.

FIGURE 32. Serous (left), mucous (middle), and mixed (right) acini of a human tracheal gland 900 ×.

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Blood

Blood is a cell-containing fluid which transports oxygen, water, food materials, metabolic waste products, and internal secretions. It is a tissue, closely related to connective tissue. Because it is constantly circulating throughout the body, it serves to integrate one part with another. Blood provides a means by which the internal environment is maintained constant. Furthermore, it is the vehicle for quickly mobilizing defenses against trauma and disease. It is a short-lived tissue, all the cells of which are replaced a great many times during a normal human life.

PLASMA

Blood, as a tissue, has interstitial substance, the **plasma**, in which its cells, unattached to one another, are suspended. Blood forms 7 to 8 per cent of the weight of the body. Consequently, a person weighing 75 kg. has about 6 l. of blood. Almost 55 per cent, or at least 3 l. of this, is plasma. The total volume of plasma is maintained with remarkable constancy and, in emergencies, at the expense of tissue fluid and lymph. To the beginner, blood plasma looks like an insignificant watery background material. To the biochemist and general physiologist, it is a veritable gold mine of protein fractions. The extensive employment of dehydrated plasma to replace proteins lost by hemorrhage from war wounds serves to illustrate the physiological importance of this anatomically insignificant fluid component of the tissue, blood.

FORMED ELEMENTS

Formed elements of the blood are **red corpuscles**, white corpuscles or **leucocytes**, and **blood platelets**. These are all illustrated in Figs. 33 and

34. Red corpuscles are most numerous, 4.5 to 5 million being present in each cubic millimeter of blood. Thus, there are about 30 trillion red corpuscles in the entire body. The leucocytes are much less numerous, about 8,000 per cubic millimeter. Platelets number 200,000 to 400,000 per cubic millimeter of blood.

Techniques for determining numbers of corpuscles, the amounts of hemoglobin, and the proportion of formed elements and plasma will be considered in other courses. They are standard practices but often conducted with amazing inaccuracy. To do justice to them requires considerable training and skill and certainly more time than the usual course in histology permits.

The formed elements of the blood separate from the blood under the influence of certain constituents of the plasma and blood platelets to form a **blood clot** when blood is exposed to air or when the endothelium of blood vessels is injured. The remaining clear yellowish fluid is known as **serum**. This should not be confused with plasma, the fluid part of unclotted blood. **Lymph** is something different again. It is a tissue fluid in lymphatic vessels. In the larger lymphatic vessels, it contains leucocytes. Lymph and plasma will clot; serum will not.

Red corpuscles: These are small biconcave discs of remarkably constant size, averaging 8.6 μ in diameter in fresh blood but only 7.6 μ in dry smears or fixed preparations. These little hemoglobin-containing cells without nuclei have remarkable properties. They are extraordinarily flexible and elastic, as can be seen in the capillary circulation of a living animal. The way they bump along, bend, and resume their normal form can be appreciated only by observing them in the living. If a demonstration cannot be set up, it is possible that motion pictures of this phenomenon may be shown.[1] Drawings of corpuscles in capillaries are reproduced in Fig. 93. The smallest vessels just fit the red corpuscles.

Red corpuscles owe their color to **hemoglobin**, a complex iron-containing protein in the cytoplasm. This pigment reflects red light and gives blood its color. However, individual corpuscles have a greenish-yellow hue. In dry smears and in sections, they are acidophilic and stain pink with eosin.

Much can be gained by observing them in fresh condition. Place a drop of blood on a slide and cover it with a cover slip. Dispersed corpuscles, presenting front and profile views, reveal their shape. In thick films of fresh blood, you may see corpuscles sticking together and resembling

[1] See Visual Aids 9 and 10

stacks of coins. These are known as **rouleaux.** If a little of the fluid is
allowed to evaporate from the preparation, you will observe the surfaces
of red corpuscles beset with conical and knob-like projections. We say
they have become **crenated.** Crenation occurs in consequence of an in-
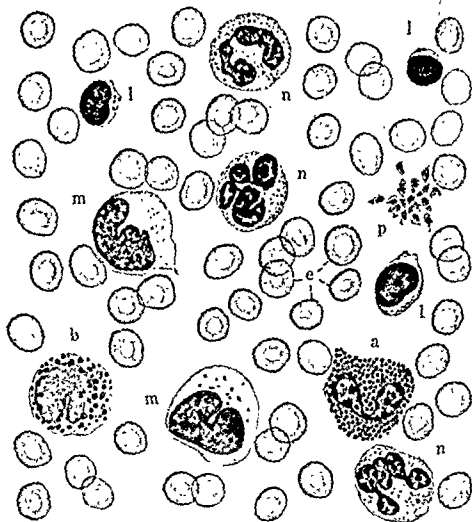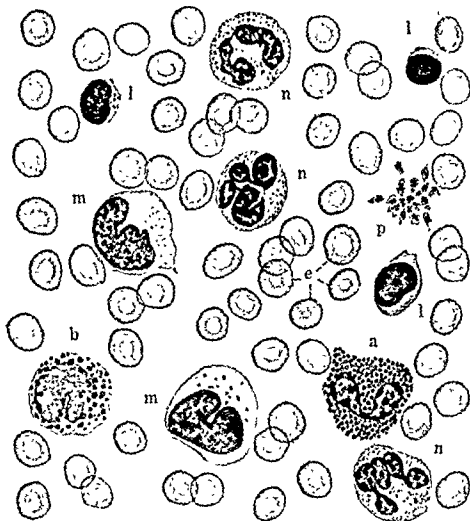

FIGURE 33. Formed elements of human blood: *a,* eosinophil; *b,* basophil;
e, red corpuscles, *l,* lymphocytes of small and medium size; *m,* monocytes,
one showing azurophil granules in the cytoplasm; *n,* neutrophils; *p,* plate-
lets. 1200 ×

crease in density of the plasma, causing it to become slightly hypertonic.
If its density is decreased by allowing water to diffuse into it, the plasma
becomes hypotonic, and the corpuscles become swollen, assume globoidal
shapes, and finally burst. This phenomenon is known as **hemolysis.** The
shadowy remains of red corpuscles consist of their delicate plasma mem-
branes, rich in lipoids. They are envelopes which contained the special-
ized, highly fluid cytoplasm.

Red blood corpuscles are constantly undergoing destruction, and new ones are added to the blood stream. Their immediate predecessors are hemoglobin-containing cells with darkly staining nuclei, found in the bone marrow but seen in circulating blood of healthy human beings only
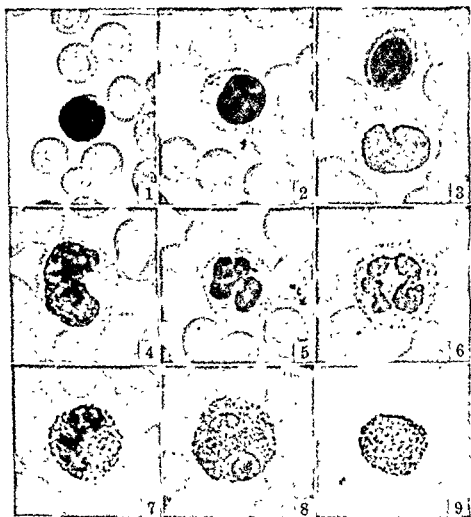
FIGURE 34. Formed elements of human blood. 1, small lymphocyte; 2, medium-sized lymphocyte with azurophil granules in the cytoplasm; 3, lymphocyte and monocyte, 4, monocyte, 5 and 6, neutrophils, 7 and 8, eosinophils, 9, basophil, platelets are present in 2 and 5, Wright's stain Photomicrographs, 1200 ×.

during early infancy. At birth, about 1 per cent[2] of the corpuscles are these nucleated cells. Nuclei disappear during development of red corpuscles. Sometimes nuclear fragments appear in blood smears, and they are called Howell-Jolly bodies. With appropriate staining, a very few

[2] Higher values have been reported, although it is doubtful if they are correct for full-term infants

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granules in the cytoplasm, even without benefit of staining. However, the use of supravital stains will aid greatly in identification of the several types. A motion-picture film[3] showing leucocytes in tissue culture is well worth seeing.

Leucocytes are studied to best advantage in thin blood smears stained with Wright's stain. For methods, consult manuals of technique. There are two categories of leucocytes, based on the presence or absence of specific granules in the cytoplasm. Those with specific granules are **granular leucocytes**; those without them, **nongranular leucocytes**. The two differ not only by the presence of specifically staining cytoplasmic granules, but also in respect to characteristics of the nucleus. The granular leucocytes have oddly shaped, often multilobulated nuclei, while the nongranular leucocytes have relatively large, spherical, or indented nuclei.

Granular leucocytes, together with all the red corpuscles and platelets, are formed in the bone marrow and constitute the **myeloid series** of blood elements. The nongranular leucocytes arise in the lymphatic organs and lymphatic tissue and are designated the **lymphoid series** of cells.

Granular leucocytes are of three kinds, differing from one another in respect to the staining reaction of their cytoplasmic granules. Those with large granules that stain intensely pink with the acid dye, eosin, are called eosinophils. Those which have large granules colored just as brilliantly with the basic dye, polychrome methylene blue, are designated basophils. The third, and by far the most numerous variety, display their very small granules faintly. These granules are neither bright pink nor dark blue, but a pale intermediate neutral shade. Consequently, the leucocytes with them are named neutrophils. Structural differences among the three are shown in Figs. 33 and 34.

Neutrophils (properly, neutrophilic leucocytes) comprise 65 to 75 per cent of all leucocytes. They are definitely larger than red corpuscles, usually measuring 10 to 12 μ in diameter. Their nuclei consist of long twisted or bent masses of darkly staining chromatin, often pinched off into several lobes. This is why some people call them **polymorphonuclear leucocytes**. Lobulation of the nucleus serves as a basis for classification into younger and older cells. Those with many lobes are considered to be old; those with one or two chromatin masses, young cells.

Neutrophils are migratory and phagocytic. They excel among all forms of leucocytes in ameboid movement. The pseudopodia of living neutro-

[3] See Visual Aids, 6.

red corpuscles, approximately 1 per cent in adults and 6 per cent in the newborn, exhibit a blue network or reticulum. These are called **reticulocytes** (Fig. 35). *Their presence at other times indicates an increased acceleration of red corpuscle production.* Few red corpuscles depart greatly from the average 7.6 μ diameter, but some large and some small forms

FIGURE 35. Reticulocytes in blood of a newborn human infant. Note also the size variations among the red corpuscles. Preparation by Dr. Q. B. DeMarsh. Photomicrograph, 1200 ×.

may be seen in blood of the newborn. These are spoken of as **macrocytic** and **microcytic** corpuscles.

The length of life of red corpuscles is 100 to 120 days. They are destroyed and phagocytized in the sinuses of the spleen and liver, for the most part. *When this occurs, the materials of which hemoglobin is constructed are not entirely cast off.* Iron is salvaged and reutilized for hemoglobin synthesis in new corpuscles developing in the bone marrow. The constant production and destruction of the red corpuscles are not unlike the constant production and destruction of cells of epithelium, mentioned in the previous chapter.

White corpuscles: These are true cells with nuclei and are properly designated, leucocytes. Their cytoplasm lacks hemoglobin and exhibits ameboid movement. In fresh blood, you can identify more than one kind of leucocyte if you study your preparations carefully. Some will exhibit

They are often more easily found outside the vascular system than in the blood. They do become numerous in the blood stream in certain parasitic and allergic diseases. Less is known about their function than about that of neutrophils. Their presence in the loose connective tissue beneath the epithelium of the respiratory and digestive tract is noteworthy. Some suggest a detoxifying role in which they absorb and remove histamine.

Basophils are the rarest of all cells in human blood. They constitute only about 0.5 per cent of the leucocytes, or 1 to 120,000 red corpuscles. Therefore, do not be overly concerned if you fail to find one in the first hour or so. If you should encounter one, you will know it, because basophils are fully as spectacular as eosinophils. The chief difference is that their large granules are stained deep blue with Wright's stain. Granules are so striking that one often overlooks the rather large, lightly stained nucleus. This is less polymorphous than that of other granular leucocytes, and it often appears to be bilobed or kidney-shaped. The granules of human basophils are water-soluble. For this reason, the cells do not show up in routine histological sections. What, if any, relationship exists between them and the mast cells of connective tissue is unknown. It will have to be added that nothing is known about their function.

The nongranular leucocytes are the lymphocytes and monocytes, which constitute the **lymphoid series** of blood cells. They may be seen in Figs. 33 and 34.

Lymphocytes are the smallest leucocytes. Most of them measure 6 to 8μ in diameter in blood smears, about the same size as red corpuscles, although some are 8 to 10μ, and a few as large as 12μ will be encountered. They are nearly one-third as numerous as neutrophils, constituting 20 to 25 per cent of all leucocytes under healthy physiological conditions. The cytoplasm is always scanty and forms just the slightest pale-blue crescent around a spherical, darkly stained, and blotched nucleus in the smaller members of this class. The cytoplasm is a little more plentiful, and the nucleus is indented in the larger circulating lymphocytes. In stained sections, the lymphocyte nucleus appears to be made up of blocks or wedges of chromatin and has somewhat of a cartwheel appearance. Larger, older lymphocytes may display a few darkly staining particles in their pale-blue cytoplasm.

Lymphocytes are actively migratory cells and show up in the most surprising places They squeeze through the endothelium of blood vessels with great facility and are found in enormous numbers in the surrounding connective tissue They even pass through the mucous mem-

phils are compared with those of lymphocytes in Fig. 36. It is probable that neutrophils do not perform any function within the blood stream. But they are not confined to the circulation. They can make their way out between the endothelial cells of capillaries and enter the tissues.

Their life in the blood is short. Evidence suggests that four days is about the maximum. What happens to them in the healthy body after that is unknown.

Neutrophils may be thought of as forming a large standing army, constantly mobilized and ever ready for body defense, for they are the first on the scene in case of infections. Infections call out reserves from the bone marrow. A marked rise in their number in the blood constitutes **leucocytosis**. Once out in the tissues, neutrophils can engulf small particles and bacteria. They appear to have a special predilection for the pyogenic organisms. Neutrophils are the shock troops, as it were, endowed with ability to kill and digest bacteria, and often to die in great numbers in doing so. They differ from other phagocytes, which are not so quick on the draw and often engulf bacteria without killing them. They are sometimes called **microphages** in contrast to the other, slower phagocytes, which are **macrophages**.
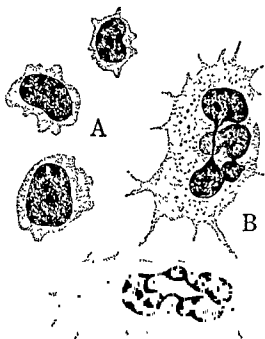
FIGURE 36. Lymphocytes, *A*, and neutrophils, *B*, in a supravitally stained preparation of fresh blood on a warm stage, showing pseudopodia extended. 1200 ×.

Eosinophils are more spectacular in appearance, although less numerous than neutrophils. They constitute 2 to 5 per cent of all leucocytes. The nucleus is usually less polymorphous, often appearing as two lobes connected with a narrow bridge. Their main characteristic feature is the presence in their cytoplasm of very prominent acidophilic granules of rather uniform size. No one with normal color vision can possibly miss these. Yet, it is common experience to find students anxious to mistake neutrophils for eosinophils. Remember, there will be 1 leucocyte to every 600 red corpuscles, but only 1 eosinophil to 20,000 red corpuscles.

Eosinophils are migratory, but apparently they are not phagocytic.

They are often more easily found outside the vascular system than in the blood. They do become numerous in the blood stream in certain parasitic and allergic diseases. Less is known about their function than about that of neutrophils. Their presence in the loose connective tissue beneath the epithelium of the respiratory and digestive tract is noteworthy. Some suggest a detoxifying role in which they absorb and remove histamine.

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branes lining digestive, respiratory, and urogenital passages of the body. Lymphocytes might well be considered primary residents of the connective tissue instead of the blood. Their life in the circulation, where they just drift about, is short—not much over one day. It has been estimated that as many enter the circulation each day as are present in it at any time. Those which are lost by migration into the lumen of the digestive tract are counted in *hundreds of millions daily*. Although lymphocytes are not phagocytic, there is growing evidence that they can become transformed into macrophages in the tissues under certain conditions. They occur abundantly in regions of inflammation. They are rather primitive cells. Their destruction by action of certain hypophyseal secretions has been observed, and this may be a source of globulin in blood plasma.

Monocytes are less numerous than lymphocytes and are larger, measuring 12 to 15 μ in diameter, or even more. The larger, older monocytes have a characteristic structure, but the smaller, younger ones are practically indistinguishable from large blood lymphocytes. The cytoplasm may be a little less basophilic, commonly containing a few purplish-stained particles. *The nucleus is eccentrically placed and is more or less deeply indented; it may be kidney- or even horseshoe-shaped in the larger monocytes* (Figs. 33 and 34).

Monocytes comprise only *2 to 6 per cent* of all leucocytes in the blood stream. But the blood stream is not their natural habitat. They are much more important cells than the small number seems to signify. In the connective tissue, they become indistinguishable from tissue macrophages. They can become enormously distended with tissue detritus or bacteria in regions of degeneration or infection. Into such regions they are marshaled more slowly than the neutrophils.

Lymphocytes and monocytes are related to each other and to other connective-tissue cells. Both are primitive elements. The interrelationship among lymphocytes, monocytes, plasma cells, tissue macrophages, fibrocytes, reticular cells, and endothelial cells appears to be quite a close one.

Blood platelets: These are tiny ovoid, biconvex bodies measuring only about 2 to 4 μ in diameter. **Platelets** are not easily observed in stained blood smears. They tend to stick to one another and to anything else with which they come in contact when blood is drawn. Careful scrutiny reveals a central, more basophilic region and a peripheral, clear, hyaline zone (Fig. 33). Platelets are not cells but simply bits of the cytoplasm of certain giant cells of the bone marrow, known as **megakaryocytes.** They play a role in the formation of blood clots, as you will learn in physiology.
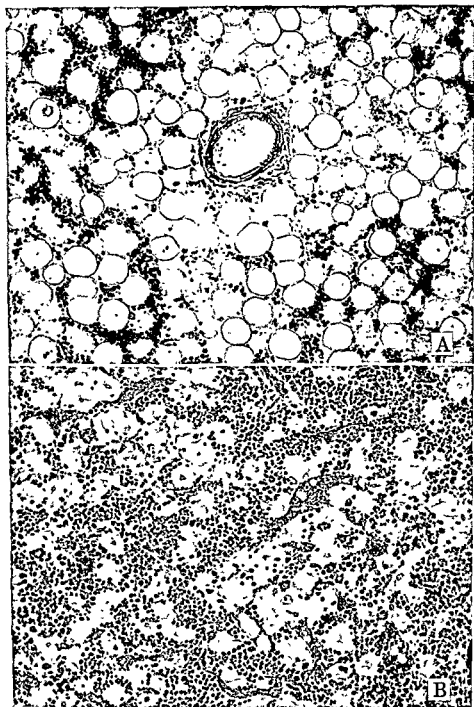
LYMPH

Lymph is not a tissue but a fluid collected from all over the body. Whatever cells it contains—lymphocytes only, under healthy conditions—are added during its passage through the lymph nodes (Fig. 93E). The composition of lymph varies according to the organ in which it arises. Thus, lymph from the liver is unusually rich in proteins. That from the small intestines contains much fat during digestion. Fatty lymph is known as **chyle**. The milky appearance of this fluid has imparted the name lacteals to the lymph capillaries of the mesenteries. Lymph joins the blood stream by way of a principal and a secondary channel, the thoracic and right lymphatic ducts. Darkfield examination of fresh blood, drawn after one has eaten a meal containing fat, reveals the presence of innumerable tiny particles of fat, known as **chylomicrons**. These were contributed to the blood by the lymph of the thoracic duct.

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   These are excellent accounts of the formed elements of the blood, easily read and full of functional considerations.

2. Downey, H. (editor). *Handbook of Hematology*; New York, Paul B. Hoeber, Inc., 1938.
   Glance through the first seven chapters. You will not have time to master much of the material, but you will see that the subject is an interesting and extensive one.

3. Ralph, P. H.: Observations on the "Normal" Adult Human Erythrocyte, *Anatomical Record*, vol. 98, pp. 489–505, 1947.
   This is a current article on a study of fresh blood with supravital stains and other techniques. It will give you a different kind of picture of red blood corpuscles.

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FIGURE 37. Bone marrow of the monkey: A, yellow marrow showing fat cells and an arteriole, B, red marrow. Photomicrographs, 150 ×.

crowded out the hemopoietic red marrow, leaving only a small island of it here and there. We may dismiss yellow marrow, for it is of little consequence compared with the red variety. When we speak of bone marrow,

Bone Marrow and Hemopoiesis

Bone marrow may be considered as a special tissue related to both blood and connective tissue. It may also be thought of as a simple organ. Its stroma is reticular connective tissue; its parenchyma, the marrow cells, of several kinds.

Looking at it as an organ, you will observe that, encased in the bones, it is well protected and of widespread occurrence. It is one of the vital organs, and a large one, too, for it comprises about 5 per cent of the body weight. It is more than twice the size of the liver. In it are formed all blood corpuscles, except lymphocytes and some monocytes. Other functions—notably, red corpuscle destruction, bone formation and destruction, and fat storage—are of secondary importance.

YELLOW AND RED MARROW

Two types of bone marrow are described in the adult, yellow and red, according to the predominance or lack of predominance of fat cells, which are found to some extent in all bony spaces. The two varieties are compared in Fig. 37. Red marrow is most abundant in young individuals and is the only type present in prenatal life. During postnatal growth, the warmer cavities of the more centrally located bones retain more of the red marrow than the cooler cavities of the peripheral long bones, which come to be filled with yellow marrow. The proportion of the two types of marrow can change in the bone through fluctuation in metabolic conditions and in temperature. Yellow marrow can be made to give way to red experimentally by locally increasing and maintaining higher temperatures.

The structure of yellow marrow is simple. It is mostly fat that has

nucleolus. These cells possess a considerable quantity of basophilic cytoplasm, which stains like that of lymphocytes. In this respect, they are unlike the reticular cells from which they arise. Few hemocytoblasts will be seen, for they are only reserve cells and do not often have to reproduce themselves. The cells derived from them are the ones that are actively
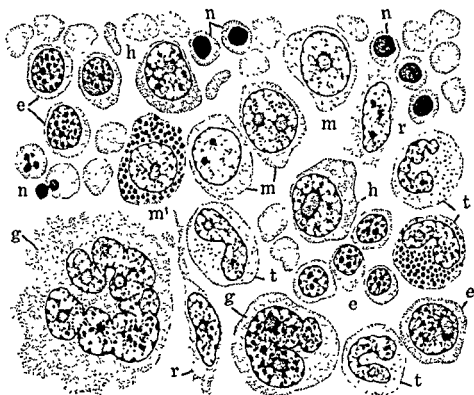
FIGURE 38. Marrow cells of a newborn kitten: *e*, erythroblasts in several stages of development, *g*, megakaryocytes, *h*, hemocytoblasts, *m*, neutrophilic myelocytes, *m'*, eosinophilic myelocyte, *n*, normoblasts, *r*, reticular cells; *t*, young granular leucocytes. Bone marrow smear preparation. 900 ×.

mitotic. It soon becomes possible to determine whether they are to give rise to red corpuscles or granular leucocytes.

Origin of granulocytes· The first cells of the leucocyte line are characterized by the appearance in their cytoplasm of a few specific granules. These cells are designated **myelocytes.** They are the most numerous cells of the bone marrow. The ones with neutrophilic granules outnumber those with eosinophilic or basophilic granules. You will not be able to see basophilic myelocytes in sections of human marrow because their granules are water-soluble and disappear in the technical procedure. Myelocytes divide mitotically to reproduce more myelocytes of their own

henceforth, we shall always mean the red, hemopoietic type unless the other is specifically designated.

Bone marrow is a soft and highly fluid tissue, as you would see if you could perform a sternal puncture. It is more solid than blood and has fibers in it. In fact, it has a **stroma,** made up largely of reticular cells and fibers. This is the framework of the organ. It is not easy to see in histological sections, because it is heavily overlaid with the marrow cells of various kinds. It lends some support to the blood vessels that enter and leave the marrow, especially the very thin-walled sinusoids.

The **marrow sinusoids** are wide and delicate capillary-like vessels, lined with cells which we may simply call **littoral cells.** They are not endothelium, for they are intensely phagocytic. Littoral cells detach themselves from the walls of the sinusoids with considerable ease and appear as free **macrophages** within the sinusoids. The walls of the sinusoids are traversed by red corpuscles and granular leucocytes which are formed in the loose fluid substance outside the blood vessels and sinusoids of the marrow. How this occurs is not entirely clear. The leucocytes, being ameboid cells, can easily work their way between the cells lining the sinusoids. The red corpuscles, on the other hand, are not ameboid. They simply pass through the extraordinarily thin protoplasmic film that lines the sinusoid and separates the tissue fluid of the marrow spaces from the plasma in the sinusoids. That is how they get into the blood.

HEMOPOIESIS IN MARROW

The precursor cells for all blood elements, including lymphocytes, are so similar that authorities have never quite agreed about them. Some hold that they are identical; others, that the two main types of leucocytes come from different stem cells, *i.e.,* myeloblasts in bone marrow and lymphoblasts in lymphatic organs. However, if one goes far enough back in development, he will find that everyone agrees regarding an ancestor common to all, which is a mesenchymal cell in the fetus and an indifferent connective-tissue cell in the adult. Let us begin the story with the cell that is derived from these and, overlooking controversial issues, consider the precursor of blood elements to be the **hemocytoblast.** The word means blood-cell former, so it is appropriate.

Hemocytoblasts, illustrated in Fig. 38, are large cells, approximately 15 μ in diameter. They have a large open nucleus with delicate strands as well as a few clumps of chromatin. The nucleus contains a prominent

They undergo many mitotic divisions, gaining hemoglobin each time and losing their basophilia. The nucleus becomes more chromatic. The cell decreases in size. Hematologists call the large early erythroblasts pro-erythroblasts. The late ones, which are smaller and retain a little basophilia, giving their cytoplasm a gray appearance, they designate polychromatophil erythroblasts. Colonies of erythroblasts and the cells de-
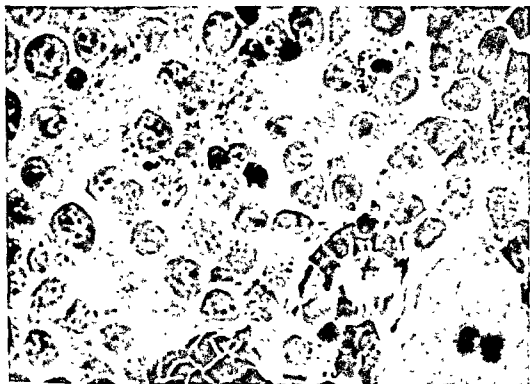

FIGURE 40. Human bone marrow (same preparation as Fig 39), showing a colony of myelocytes and young granulocytes, a megakaryocyte is seen at the lower right. Photomicrograph, 600 ×.

rived from them are encountered in sections of bone marrow. The chances are that you will not observe many isolated erythroblasts, but groups of them.

Further mitotic divisions lead to the formation of **normoblasts**. These might logically be called erythrocytes,[1] for they are cells with nuclei. They are about the size of red blood corpuscles, with acidophilic cytoplasm which is filled with hemoglobin. Their nuclei are distinctly darker and smaller than those of their predecessors. Late normoblasts have very darkly stained, pyknotic nuclei (Figs. 38 and 39). They have lost the

[1] This term is more often a synonym for red corpuscle We do not employ it for the corpuscles that lack nuclei

type. Consequently, you will see colonies of each variety in sections of
bone marrow, like those in Fig. 40.

A number of steps in the development of granular leucocytes may be
observed in Fig. 38. The basophilia of the cytoplasm of the early myelo-
cyte subsides as the specific granules increase in number. The last mitotic
divisions give rise to myelocytes that can scarcely be distinguished from
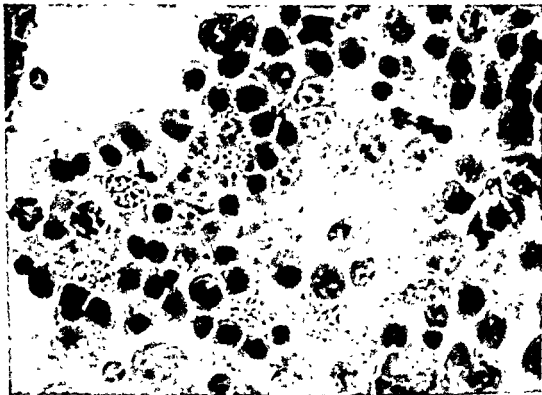
FIGURE 39. Human bone marrow section, showing a colony of normoblasts and
erythroblasts. *Specimen from Prof Balduin Lucké. Photomicrograph, 600 ×.*

young granular leucocytes. They have darkening U-shaped nuclei like
young circulating neutrophils. Hematologists give the names promyelo-
cyte and metamyelocyte to the early and late stages in differentiation of
myelocytes. Ignore them if you wish, but do keep in mind the sequence
of principal stages in formation of granular leucocytes: **reticular cell →
hemocytoblast → myelocyte → granular leucocyte.** You can easily iden-
tify all of these. They are illustrated in Figs 38 to 40.

Origin of red corpuscles. The stages in the development of red cor-
puscles comprise another major category of bone marrow cells. Some
hemocytoblasts give rise to cells with a little hemoglobin in their baso-
philic cytoplasm near the large open nucleus. It is clear that they are
precursors of red blood corpuscles. We call them **erythroblasts** (Fig. 38).

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capacity to divide and are about to become red corpuscles. How they lose their nuclei is unknown. Perhaps the nuclei simply dissolve. Some believe that they become fragmented and that these fragments as well as whole nuclei are extruded from the normoblast cytoplasm. The remaining, nonnucleated cells are erythroplastids or, better, **red blood corpuscles.**

When first produced in the marrow, red corpuscles may exhibit a cytoplasmic reticulum when supravitally stained. These are called **reticulocytes.** Approximately 1 per cent of adult circulating red corpuscles are reticulocytes. Keep clearly in mind that a reticulocyte is a red blood corpuscle, but a reticular cell is a connective-tissue cell of a primitive kind.

To summarize, the following stages in the development of red blood corpuscles are identifiable in any well-stained section or smear of bone marrow: reticular cell → hemocytoblast → erythroblast → normoblast → **red blood corpuscle.**

Origin of blood platelets: The study of bone marrow would be easy, indeed, if the cells were as readily identified as the **megakaryocyte.** Aside from its very large size, ranging up to 40 μ in diameter, and its ragged outline, the megakaryocyte is characterized by an irregularly lobulated and giant nucleus (Fig. 38). Young megakaryocytes with less complicated nuclei will be found. They, too, arise from the hemocytoblast.

Megakaryocytes extend their cytoplasmic pseudopodia through the walls of the narrow sinusoids. There, it is said, they bud off and float away in the blood stream as **blood platelets.** Megakaryocyte cytoplasm is slightly granular, as is that of the platelets.

Other cells of bone marrow: Other giant cells may be seen in the bone marrow, especially the marrow of spongy bone and that of young individuals. These cells are the multinucleated **polykaryocytes,** known also as **osteoclasts** in regions of bone growth (page 103). **Osteoblasts,** too, may be seen in these locations. The presence here and there in bone marrow of the ubiquitous lymphocyte should be borne in mind. This does not mean that the lymphocyte arises in the bone marrow. On the other hand, a few **monocytes** of local origin may be encountered.

It is always a matter of considerable surprise in studying bone marrow to find that the number of cells in the granular leucocyte line is so great in proportion to the number in the red corpuscle line. In circulating blood, there are approximately 800 red corpuscles to every granular leucocyte. Why does not a similar numerical relationship exist in the bone marrow, where both of these elements are formed? The red corpuscles

form quickly and get on out into the circulation, where they live much longer than leucocytes. The precursor cells of granular leucocytes live longer between mitotic divisions in the bone marrow, so there are nearly three times as many myelocytes as erythroblasts.

HEMOPOIESIS IN LYMPHATIC TISSUE

We shall consider the formation of nongranular leucocytes now, even though this occurs outside of the bone marrow in lymphatic tissue, the structure of which will be described in Chap. 11. Reticular cells of the stroma of lymphatic tissue, especially in germinal centers of lymph nodules, free themselves and develop basophilic cytoplasm. Thus, they become **hemocytoblasts**. After this, you cannot see any difference between them and the hemocytoblasts of bone marrow. These large cells, about 15 μ in diameter, are not numerous.

They divide into other cells which are a little smaller, and to which it is reasonable to give the name **lymphoblast**. Some authors call them large lymphocytes, but we shall reserve that term for medium-sized and small cells with very dark nuclei—the sizes that can circulate in the blood stream. Lymphoblasts have a somewhat darker nucleus than hemocytoblasts. It is smaller but occupies more of the cell. Lymphoblasts can divide mitotically an indefinite number of times, usually increasing slightly in size after each division.

As size decreases and the nucleus becomes more chromatic, they become indistinguishable from **lymphocytes** of the blood or connective tissue. Great numbers of lymphocytes enter the small lymph vessels and are transported to the vascular system by way of the thoracic duct and the right lymphatic duct.

Lymphocytes in tissues have not lost their capacity for division. The little ones can increase in size. You cannot tell them from lymphoblasts then. After attaining a certain size, they undergo mitosis.

Under certain abnormal conditions the stem cells of lymphatic tissue can develop specific granules and give rise to granular leucocytes. Under other pathological conditions they can become malignant forms. However, in the more usual course of events, they engage in activities about which we know too little. Their capacities to respond to the call of inflammation and to give rise to macrophages in the tissues are noteworthy.

The **monocyte** appears to be no more nor less than one form of macrophage, which is one of the principal cells of connective tissue. It may be

recognized in many places and has been described in the blood in the preceding chapter. It seems clear that monocytes can arise from the same cells that form the other cells of blood; perhaps also from lymphocytes themselves. Under the proper stimuli, they can arise from reticular and other primitive cells in such places as the spleen, liver, and bone marrow.

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   The several points of controversy concerning hemopoiesis are considered in this. The last two pages on comparative hematology offer interesting information not covered in the present book.

2. Wislocki, G. B., H. Bunting, and E. W. Dempsey: Further Observations on the Chemical Cytology of Megakaryocytes and Other Cells of Hemopoietic Tissues, *Anatomical Record*, vol. 98, pp. 527–537, 1947.
   This describes a new approach to the study of origin of blood platelets.

Connective Tissue

Connective tissue is quite unlike either of the tissues you have studied. It has only a small proportion of cells, and its tissue fluid constituent is commonly overlooked by the histologist. It is the interstitial matrix substance and especially the fibers in the matrix that characterize connective tissue.

The matrix starts out as fluid in the embryo. As development takes place, chemical compounds that are added to it begin to give it a consistency. In some regions of the adult, this amounts to no more than a barely perceptible viscosity, but elsewhere, e.g., in cartilage and bone, the matrix becomes solid. Fibers are always included in the matrix substance, although they are less noticeable in cartilage and bone than other varieties of connective tissue. There are several kinds, and they are arranged in various ways, imparting individual characteristics to the varieties of connective tissue.

As the name implies, connective tissue serves to connect one part of the body with another. Most histologists recognize two main groups. One connects and keeps the various components of the body from falling apart. The other supports the softer parts and keeps the organism from collapsing like a beached jellyfish. Some neglect to mention that an equally important function of connective tissue is to separate one group of cells from another, spacing them so that they may function to better advantage.

Connective tissue proper, when encountered in the dissecting laboratory, is called **fascia**. It is the stuffing, padding material underneath the skin, between the muscles, and along the nerves and blood vessels. In other words, it is the material, removal of which occupies so much of the young anatomist's time. Too often, he is permitted to think of it as

something with little more than nuisance value, when, in truth, it is one of the most important constituents of the body. Its role in the healing of wounds and in the defense reaction is of major importance. Furthermore, through its interstitial fluid pass most of the metabolic substances to and from the working cells of the body.

EMBRYONIC CONNECTIVE TISSUE

The source of all connective-tissue cells is **mesenchyme**, the highly cellular tissue that fills spaces between epithelial layers in young embryos. This kind of connective tissue consists of branched, irregularly shaped cells forming a meshwork, the spaces of which are filled with interstitial fluid. Mesenchymal cells are illustrated in Fig. 41. The extended processes of the cells seem to be continuous with those of adjacent cells, but actually they make contact only. A true syncytium is not formed.

This embryonic connective tissue does not persist long, but some adult tissues resemble it, notably the reticular connective tissue. It is probable that a few widely dispersed cells with all the potentialities of mesenchymal cells exist throughout life. They offer a source of replacement for connective tissue and blood elements. Because of their resemblance in sections to other cells of adult connective tissue, it is impossible to recognize these **indifferent cells**.

CHARACTERISTICS OF CONNECTIVE TISSUE PROPER

Connective tissue proper, excluding cartilage and bone, forms the subject of the present chapter. In varying proportions, the three constituents —cells, fibers, and interstitial substance—are found in all varieties. The cells of greatest significance fall into two principal groups: those associated with fiber formation and the repair of wounds and those functioning in the defense reaction of the body. A few other cells deserve honorable mention, but we shall consider them later. Three types of fibers are encountered in connective tissue. They are the most prominent components.

Connective-tissue fibers: Associated with the cells of reticular connective tissue (Figs. 42 and 51), and more rarely encountered elsewhere, are the **reticular fibers**. With special stains, they can be seen in the walls of blood vessels and around closely packed fat cells (Figs. 43 and 58). They are delicate structures staining intensely with certain silver methods. For

that reason, they are often called **argyrophilic fibers**. They differ chemically from other fibers in connective tissue, although they are closely related to collagenous fibers and merge with them in some places, as shown in Fig. 43. More about them later (page 79).

The fibers predominating in fibrous connective tissue are known as **collagenous** because they yield collagen, a form of gelatin, after pro-
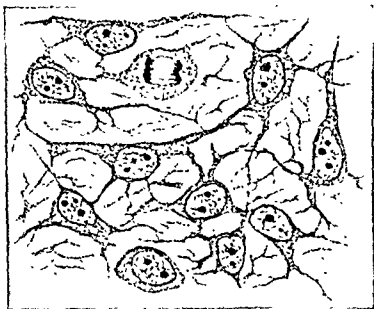
FIGURE 41. Mesenchyme in a 60-mm. dog fetus. Silver stain. 1200 ×.

longed boiling. Glue is made from them. These fibers are made up of many fine fibrils that do not branch, although the fibers that they form do branch. In the fresh state, the tissue containing them appears white. Consequently, the collagenous fibers are commonly called **white fibers,** and the tissue in which they abound is white fibrous connective tissue. They resist stretching and impart strength to structures composed of connective tissue. They are the fibers of ligaments and tendons.

A third type of fiber in connective tissue, the **elastic fiber,** differs chemically from the preceding two. Elastic fibers in sufficient mass have a yellowish color and are then called **yellow fibers.** They occur as isolated branching threads among collagenous fibers in loose connective tissue, also as plates or membranes in arteries. The great ligament of the neck of grazing animals is made of enlarged elastic fibers. Special stains are required to differentiate elastic from other fibers. Figure 52 shows them beneath the epithelium of the tongue.

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C is restored to the diet. The fibroblasts and their intracellular fibroglia fibrils appear to be unaffected, and it is not clear that they engage directly in the production of the new collagenous fibers. Beyond this we can say very little at present. Figure 44 illustrates the appearance of young collagenous fibers in a fetus.

The formation of reticular fibers may be similar to that of the col-
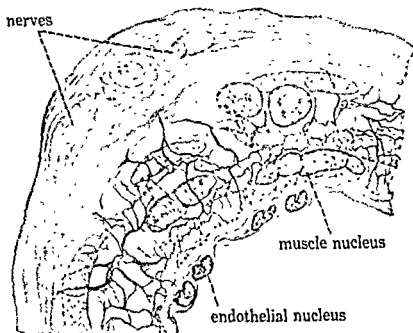
FIGURE 43. Reticular fibers in the wall of an arteriole. Note their connection with the collagenous fibers of the tunica adventitia. Silver carbonate stain. 900 ×.

lagenous fibers. Reticular fibers are continuous with, and can become, collagenous; therefore, they may be considered immature forms of the latter. Nothing is known about elastic fiber formation.

Interstitial matrix and fluid: The intercellular substance of connective tissue proper consists of **tissue fluid** and some very inconspicuous jelly-like material, somewhat resembling the intercellular cement of epithelial cells. This **matrix** binds the collagenous fibrils together in fibers. It is deficient elsewhere in the connective tissue of the adult, leaving only fluid-filled spaces. In the young individual, it seems to be continuous throughout the connective tissue. Wharton's jelly of the umbilical cord is formed largely by this matrix. In cartilage and bone, matrix becomes the main component and is solidified.

The interstitial substance of connective tissue is of great functional

The cells associated with the formation of collagenous fibers have been called fibroblasts in the belief that they produce the fibers. To be sure, certain fine **fibroglia** fibrils can be observed in their cytoplasm when appropriate staining methods are used. However, the functional fibers of
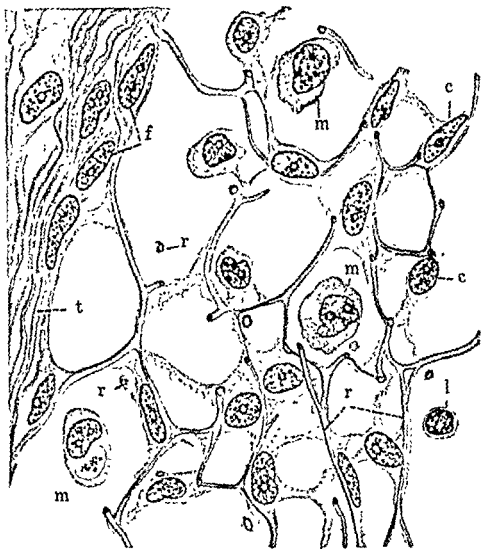
FIGURE 42 Reticulum of a lymph node, adult cat (lymphocytes have been washed away) c, reticular cells, f, fibroblast nuclei in t, trabeculum of collagenous fibers, l, lymphocyte; m, macrophages; r, reticular fibers. 900 ×.

connective tissue arise outside of cell bodies in the intercellular matrix substance. Some evidence suggests that cytoplasmic substance, extruded from the surface of the fibroblast, engages in the process of fiber production.

The formation of collagenous fibers ceases when animals are deprived of vitamin C until they become scorbutic. It begins again when vitamin

pair the damage. In a sense, they resume the life they led during embryonic development.

Macrophages are the principal phagocytic cells of connective tissue. They are big, actively ameboid cells, as large as monocytes or larger.
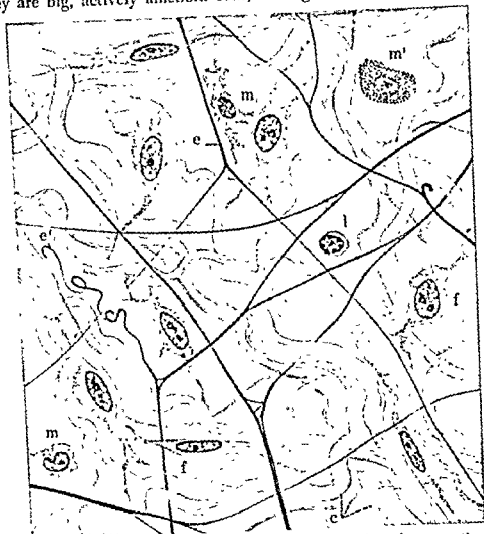
FIGURE 45 Teased preparation of supravitally stained areolar connective tissue of a kitten c, collagenous fiber bundles, e, elastic fibers, f, fibroblasts, l, lymphocyte, m, macrophages, m', mast cell 900 ×.

As a matter of fact, macrophages and monocytes are simply slightly different varieties of the same thing. The reason one does not see macrophages in the blood stream is that they are too big and sticky to go through the smallest capillaries and are quickly filtered out.

The macrophage nucleus is much darker, appreciably smaller, and more irregular than that of the fibroblast. It has a greater amount of chromatin in it, arranged in coarse particles. In ordinary histological sec-

significance. A considerable part of the body water exists there. Through it must pass, between blood and cells, the nutritive and metabolic materials. Anyone who has had experience with the subcutaneous injection of drugs will realize the promptness, with which materials in the *interstitial substance* reach the blood stream and brain.

Connective-tissue cells: The cells of connective tissues are relatively
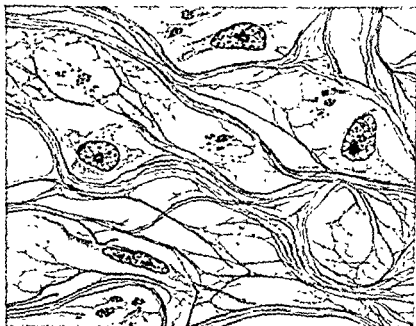
FIGURE 44. Young collagenous fibers and fibroblasts in the jaw of a 7-month human fetus. 900 ×.

few and inconspicuous. During most of the time, they have little to do and simply lie in wait to prove their importance.

Fibroblasts, seen in Figs. 44 and 45, closely resemble mesenchymal cells, from which they are descended. They occur stretched out among fibers of connective tissue and with their processes often clasping the fibers. These processes are well shown with certain silver stains (Fig. 46). Their cytoplasm is usually difficult to see with ordinary staining methods. They can be recognized by their nuclei, which are slightly elongated, contain little chromatin, and are stained lightly with hematoxylin. The nuclei resemble those of endothelial cells but do not look like the other connective-tissue cell nuclei.

The function of fibroblasts has been discussed (page 70). Just how they form fibers, we do not know. Tissue injury apparently releases substances that stimulate fibroblasts to become more active. They then can undergo multiplication and engage in the formation of scar tissue to re-

microglia. Regardless of name or location, these phagocytic cells are similar. Examples of macrophages showing activity appear in Fig. 47.

Most, but not all, of the endothelial-like cells lining the sinuses of bone marrow and lymphatic organs, and many among the reticular cells of
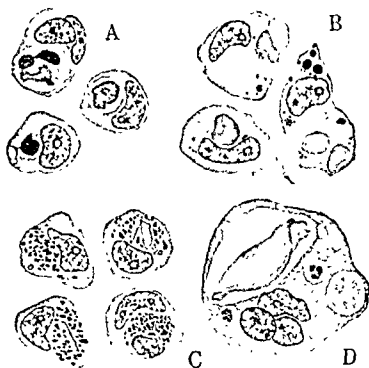
FIGURE 47 Phagocytosis by macrophages: A, leuco-
cytes present in the cytoplasm of lymph-node macro-
phages of the cat, B, red blood corpuscles and blood pig-
ment in the cytoplasm of liver macrophages in human
malaria, C, carbon and silica particles in the cytoplasm
of lung macrophages of a monkey, one has engulfed an-
other degenerating carbon-laden phagocyte, D, multinu-
cleated macrophage or foreign-body cell, from vaginal
smear of a guinea pig Preparation by Dr G N. Papani-
colaou. 1200 ×.

myeloid and lymphatic tissue, are strongly phagocytic. They, too, are macrophages. These endothelial-like cells and reticular cells are often spoken of as **reticuloendothelial** cells. There is little reason to continue to grace them with this specific name. They are macrophages, like all the rest.

The origin of macrophages is of some importance. There is sometimes great and sudden need for large numbers of these elements in the defense of the body. Some may arise by mitotic division of existing macrophages.

tions, you will see little of the cytoplasm. It extends out in processes among the fibers of healthy connective tissue, but when there is a call to activity, as in inflammation, the processes are pulled in and the macrophages appear as ovoid cells. It is customary to speak of fixed (*i.e.*, anchored) macrophages and free macrophages. Vacuoles and phagocytized materials may be seen in their cytoplasm in Figs. 42 and 45. Macro-

FIGURE 46. Fibroblasts and collagenous fibers in a dog's tongue. Silver stain. 900 ×.

phages are just about as numerous as fibroblasts in most loose connective tissue.

The macrophage has been called by more names than any other cell in the body. Many histologists designated it **histiocyte**, which is too vague because the term means "tissue cell." Other names that we do not intend to employ are clasmatocyte, resting-wandering cell, adventitial cell, rhagiocrine cell, endothelial leucocyte, and polyblast. They are all one and the same.

In various regions, macrophages have been given special names. In lymphatic organs and bone marrow, some are called littoral cells; in spleen they are splenocytes; in liver, Kupffer cells; in the lung alveoli, dust cells, in the blood, monocytes; and in the brain and spinal cord,

cells, fibroblasts and macrophages, it is recommended that time-lapse motion pictures be demonstrated.[1] A much better conception of these cells will be gained in this way than by studying fixed and stained preparations of connective tissue.

A number of other cells are encountered in loose connective tissue, some in greater numbers in one place than in another. In ordinary his-
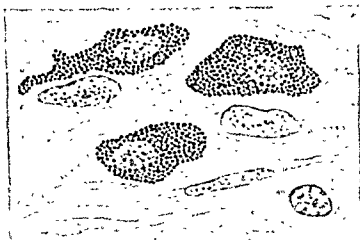
FIGURE 49. Mast cells in the capsule of a human palatine tonsil. One lymphocyte and three fibroblasts may be seen but are very lightly stained. 1200 ×

tological preparations, you will often observe **lymphocytes.** They come from the blood but are to be found almost everywhere. They are the smallest cells in connective tissue. Where they become very numerous among reticular cells, they form lymphatic tissue (page 155).

A somewhat similar cell, and one that may represent a stage in the degeneration of the lymphocyte, is the **plasma cell.** Its nucleus resembles the lymphocyte nucleus and has blocks of chromatin that give it an irregularly checkered appearance. The basophilic cytoplasm is more plentiful than that of the lymphocyte and may display a washed-out area near the nucleus. Figure 48 illustrates plasma cells, lymphocytes, and fibroblasts.

Eosinophils are encountered in connective tissue, especially beneath the mucous membrane of digestive and respiratory tracts. They, too, wander in from the blood.

Mast cells will not be seen in routine preparations because the large basophilic cytoplasmic granules that characterize them are water-soluble

[1] See Visual Aids 1, 3, and 7.

Others, as we have said, may come from monocytes and these in turn from lymphocytes. Some may arise from indifferent, essentially mesenchymal cells scattered through loose connective tissue. One of the most important sources of macrophages seems to be lymphocytes. In regions of inflammation, lymphocytes swarm out of the capillaries, and soon the surrounding tissue becomes filled with macrophages.
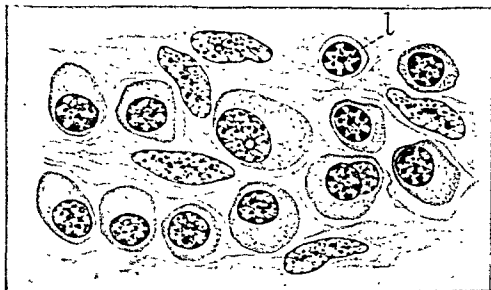
FIGURE 48. Plasma cells and one lymphocyte, *l*, in the lamina propria of a cat's small intestine. Elongated nuclei belong to fibroblasts. 1200 ×.

As was pointed out in Chap. 4, monocytes and macrophages are called into action more slowly than are the other phagocytic cells, the neutrophils of the blood. Neutrophils get to the scene first and engage the enemy, slaughtering him left and right. Macrophages come in later and mop up. They stop at nothing. When a macrophage encounters a foreign particle too big for it to handle alone, it joins forces with other macrophages to form a giant macrophage, like that illustrated in Fig. 47*D*. Such cells are called foreign-body cells. This is a term that refers to nothing more than a multinucleated macrophage.

Although macrophages in loose connective tissue and in the brain seem not to have much to do during normal healthy conditions, those in a few locations are kept very busy phagocytizing the products of physiological degeneration. To the macrophages of the bone marrow, liver, and spleen falls the task of disposing of worn-out blood corpuscles and fragments of corpuscles. It is remarkable that they never attack healthy cells but only those whose functional lives are spent.

For the study of the movements of the two principal connective-tissue

TYPES OF CONNECTIVE TISSUE

The appearance and characteristics of connective tissue vary considerably in different locations. It is possible to classify this tissue according
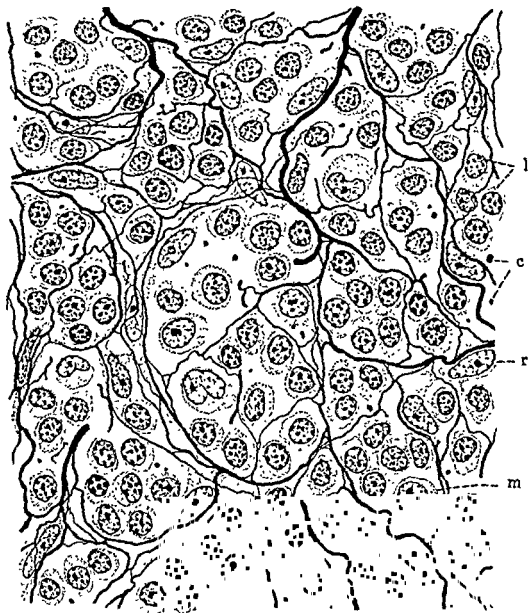
FIGURE 51 Reticulum of a splenic nodule. *c*, reticular fibers in cross section, *l*, lymphocytes, *m*, macrophage, *r*, reticular cell. Silver carbonate stain. 900 ×

to fiber type and density and, to a lesser extent, according to its cellular organization.

Reticular tissue: One of the tissues in which argyrophilic reticular fibers

and are washed out in preparing the tissues. It is uncertain whether they are identical with the basophils of blood. *Figure 49 illustrates a group of them.*

Specialized cells of several kinds may be found in connective tissue. **Pigment cells** commonly occur in the iris and chorioid of the eye, in various other locations, and beneath the epidermis of dark-skinned races.

FIGURE 50. Pigmented cells in the stroma of the iris of a rabbit's eye. 900 ×.

Some are shown in Fig. 50. **Fat cells** are encountered in the connective tissue of many localities. Since their presence in considerable numbers gives rise to a special variety of connective tissue, they will be considered separately (page 85).

The presence in connective tissue of **indifferent cells**, related to cells of mesenchyme, should be borne in mind. Although these cannot be readily differentiated from other cells, they are important and serve as replenishers of all types of connective tissue and related cells.

In summarizing the general characteristics of connective tissue proper, the following points should be stressed: Cells are few and fibers numerous. Intercellular substance is of great importance, but relatively inconspicuous. Fibers are of three types, although the collagenous are by far the most numerous and important. A few elastic fibers intermingle with these but are especially prominent in artery walls. Reticular fibers are encountered in restricted localities. Cells of connective tissue are principally fibroblasts and macrophages; indifferent cells are present among them; most others are just occasional visitors from the blood. Interstitial substance is tissue fluid, with a little jelly-like matrix sticking fibrils together.

FIGURE 52. Elastic fiber network in the lamina propria of the lingual mucous membrane of a rabbit Stained for elastic fibers 900 ×

thelial tissue of the tongue. The cells are mainly of the fibroblast type, although macrophages can be found Other varieties are rarely seen.

Fibrous connective tissue forming the corium of the skin is dense (Fig.

predominate in place of coarser collagenous fibers is **reticular connective tissue.** They arrange themselves in delicate lattice-like frameworks, which serve to support such cells as lymphocytes and fluid-borne colonies of hemopoietic cells. The arrangement of argyrophilic fibers, reticular cells, and lymphocytes is shown in Fig. 51 (see also Fig. 42).

Reticular tissue is found in other places than the bone marrow and lymphatic organs. It may be seen in the basement membranes of epithelium, in compact fat, in a loose layer beneath mucous membranes of digestive and respiratory passages, in some of the endocrine organs, and in the walls of blood vessels.

When the lymphocytes of a lymph node are washed away, the cells of reticular tissue present a primitive appearance like those of mesenchyme. Their processes extend out along the reticular fibers. In some places, reticular cells line blood and lymph sinuses and resemble endothelium. Some serve only as lining cells or supporting cells, but many have developed phagocytic characteristics and have become macrophages. Thus, there are nonphagocytic cells associated with reticular fibers, not unlike the fibroblasts of collagenous fibers; and there are phagocytic cells, indistinguishable from other macrophages, in this rather simple form of connective tissue.

Loose fibrous connective tissue: Loose fibrous connective tissue is usually called **areolar tissue.** It may be considered the prototype of all connective tissue. In it are a few elastic fibers, but the collagenous fibers abound. The fibers are arranged in no particular pattern. They run in all directions and form a loose meshwork full of tissue fluid spaces.

Areolar tissue is the most widely distributed connective tissue. It accompanies the blood vessels and nerves, which go almost everywhere. It extends in and out among the components of most organs, glands, and muscles. It is found beneath most mucous and serous membranes. A description of its components would only duplicate the general description of fibers, intercellular substance, and cells of connective tissue in general, which has been presented in this chapter. Figure 45 illustrates the appearance of a spread preparation of areolar tissue. You will find it profitable to attempt to duplicate it, using the subcutaneous tissue of any small animal for this purpose.

Dense fibrous connective tissue: In many places, the collagenous fibers of connective tissue increase in size and number and tend to crowd out the tissue fluid and cells. The role of elastic fibers in **dense connective tissue** is usually quite secondary. Figure 52 shows them in the subepi-
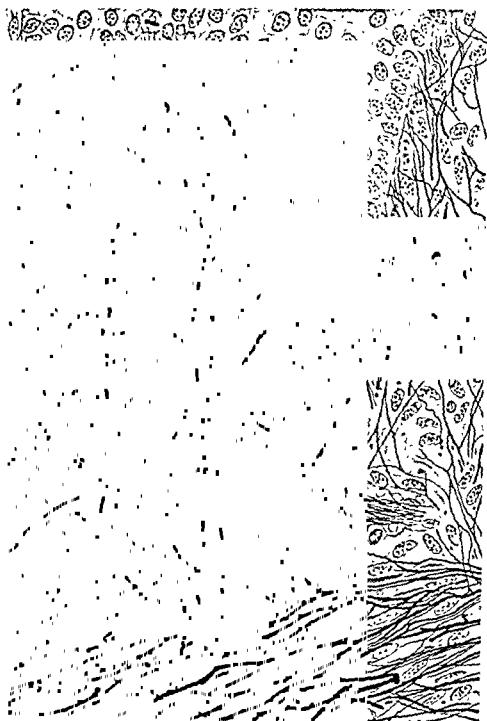
FIGURE 52. Elastic fiber network in the lamina propria of the lingual mucous membrane of a rabbit. Stained for elastic fibers. 900 ×.

thelial tissue of the tongue. The cells are mainly of the fibroblast type, although macrophages can be found. Other varieties are rarely seen.

Fibrous connective tissue forming the corium of the skin is dense (Fig.

FIGURE 53. Collagenous fibers of dense connective tissue in the corium of thick human skin Note blood vessels at the bottom Photomicrograph, 600 ×.

53). The fibrous capsules of some organs, such as the spleen and testicle, are good examples of this tissue. Some rather heavy membranes like the dura mater of the brain (Fig. 149), the periosteum of bone, and perineurium surrounding bundles of nerve fibers are similarly composed. The heart valves and the rings of the cardiac orifices likewise are constructed of dense fibrous connective tissue.
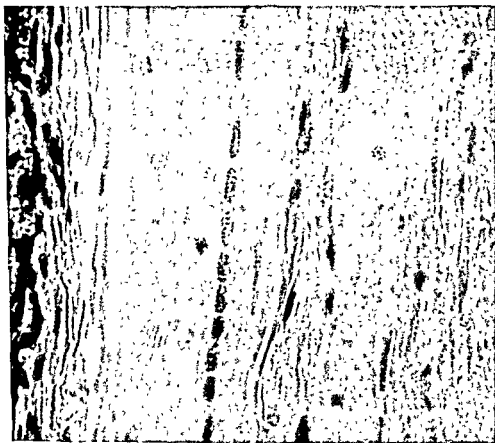
FIGURE 54 Rows of tendon-cell nuclei in a longitudinal section of tendon. Less compact connective tissue of the peritendineum with blood vessels is seen at the left Photomicrograph, 600 ×.

The gradation from areolar tissue to dense fibrous connective tissue is gradual. The two types are not distinctly differentiated from each other.

A special kind of dense fibrous connective tissue occurs in the cornea of the eye, where transparency has been attained. The stroma of the ovary is made up of another special variety, in which cells are extraordinarily numerous. In other locations, collagenous fibers are lamellated, as in some of the sensory nerve endings. Great density of fibers and orderly arrangement of them will be seen in ligaments, aponeuroses, and tendons.

Tendon: In ligaments and tendons, we see the densest form of fibrous connective tissue. **Tendons** are constructed of parallel collagenous fibrils, bundled together compactly and clasped by wing-like protoplasmic pro-

FIGURE 55   Tendon in cross section, showing cells with wing-shaped projections   Note the pentendinal septa   Photomicrograph, 600 ×.

jections of the tendon cells. These cells, related to fibroblasts, form longitudinal rows as indicated in Fig. 54. They are compressed by the surrounding tendon fiber bundles so that they resemble thin rods in profile view but are stellate in cross section. Figure 55 is a photomicrograph showing this arrangement

Tendons are ensheathed by dense fibrous connective tissue of the less

specialized type. Septa, as seen in Fig. 54, subdivide tendons. The sheaths and septa of tendons are continuous with the sheaths and septa of muscles at the myotendinal junctions. Blood vessels and nerves traverse them to enter the tendon. However, the blood supply of tendons is not rich, and healing is accomplished slowly after injury.
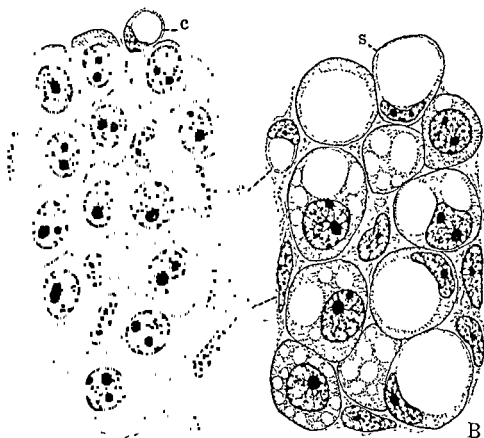
FIGURE 56 Development of adipose tissue in two regions, A and B, in the larynx of a newborn kitten c, blood capillaries, f, fibroblast nuclei, s, signet fat cell 900 ×.

Aponeuroses and **ligaments** are constructed like tendons but are of different shapes, and their fibers are less compactly arranged.

Adipose tissue. Cells containing large amounts of fat in the cytoplasm are found in connective tissue almost everywhere throughout the body. In many localities, they are so closely packed that the tissue appears to be composed exclusively of these elements There they are suspended in a meshwork of fine collagenous and reticular fibers and have a rich vascular supply. The resulting aggregation is called **adipose tissue.**

Strands of adipose tissue accompanying blood vessels can be studied to advantage in the fresh condition In a mesentery of the intestine of any
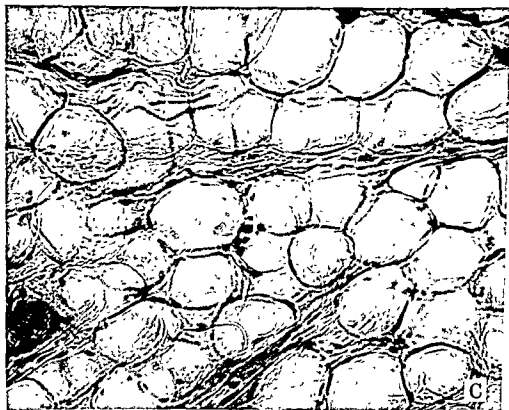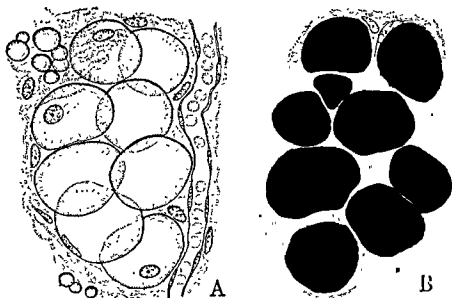
FIGURE 57. Adipose tissue. A, in a fresh preparation of a kitten's mesentery; note extruded fat droplets at the upper and lower left; B, in connective tissue around a nerve (osmic acid stain), C, photomicrograph of human subcutaneous adipose tissue 300 ×.

small animal, fat cells look like large oil drops. Supravital staining will reveal the nuclei of some of them. The cytoplasm extends as a thin film around each drop.

The structure of fat may be understood better by following its development (Fig. 56). Development is not confined to prenatal life. It is apt to vex us in middle age. In the fetus, groups of mesenchymal cells withdraw their processes to become ovoid in shape in regions where capillary vessels abound. Soon, small droplets of fat appear in the cytoplasm, merging
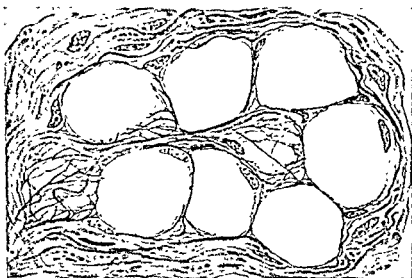
FIGURE 58 Adipose tissue of a dog, showing reticular fibers—the fine black lines—around fat cells. Silver carbonate stain 300 ×.

into larger droplets until a single big drop almost fills the cell. This displaces the nucleus to the periphery and stretches the cytoplasm into a thin membrane. Cells of this kind represent the final stage in development. When sectioned through the nucleus, they are called signet cells. In the mesentery, stained whole, they appear as in Fig. 57A; with osmic acid, in 57B; in a section, in 57C.

Fat is removed from adipose tissue by alcohol and other solvents used in making histological preparations. Consequently, sections reveal only large empty spaces where the fat used to be. Fat cells are so large and the histological sections so thin that fat-cell nuclei are rarely included in sectional view (Fig. 58). Such a preparation of compact adipose tissue may look like an empty sponge and bear little resemblance to the adipose tissue of a living animal (Fig. 57A).

Not only does adipose tissue provide a store of fat for reserve energy and metabolism, by accumulating in layers beneath the skin, it forms

an excellent insulation against heat loss and a very adequate lightweight padding material. It should not be thought of as a depot for dead storage of fat, to be used by the body only at some time in the distant future. There is a continuous and rapid turnover in storage and utilization of this material. The rich capillary blood supply of fat plays an important part in this.

It is known that fat is stored more promptly in the subcutaneous tissue and the omentum than in other localities. Connective tissue in the eyelids and scrotum never stores fat. During starvation, some connective tissue gives up fat more readily than others. The acquisition and elimination of fat from connective tissue are regulated in a precise manner by hormones from a number of the endocrine glands, especially the hypophysis and the thyroid.

During the early years of life, some adipose tissue, notably that in the posterior body wall near the kidneys, is made up of cells whose fat droplets do not flow together to comprise typical fat cells. The high degree of vascularity gives this cellular adipose tissue a brown tint, called **brown fat**. Similar tissue is encountered in certain hibernating animals.

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2. Sterns, L.: Studies on the Development of Connective Tissue in Transparent Chambers in the Rabbit's Ear, *American Journal of Anatomy*, vols. 66 and 67, pp. 133–176 and 55–97, 1940.
   Your attention is directed especially to Dr Sterns's account of the development of fibers. This begins on page 69 of the second article

3. Schmitt, F O, C E. Hall, and M. A. Jakus Electron Microscope Investigations of the Structure of Collagen, *Journal of Cellular and Comparative Physiology*, vol. 20, pp 11–33, 1942.
   This will bring you up to date on the subject of collagenous fibers. The electron microscope provides a remarkable tool to extend the horizon of the light microscope.

Cartilage, Bone, and Joints

Cartilage and bone are closely related to fibrous connective tissue. They are composed of the same three elements: fibers, cells, and interstitial substance. They form the skeleton and are often classified together as supporting tissue. The importance of cartilage and bones, especially the latter, goes beyond structural support. Their role in mineral metabolism is particularly noteworthy.

CARTILAGE

Cartilage or gristle has specialized in the direction of rigidity, yet retains some flexibility and resiliency. Cartilage forms the skeleton of the lower vertebrate animals as well as that of mammalian fetuses. It has been replaced largely with bone and plays only a minor role in the adult. It is one of the least useful constituents of the adult body but was indispensable in the young for successful bone growth.

Cartilage is simpler than fibrous connective tissue and differs in several respects. The cells are all of one kind, called **chondrocytes.** The interstitial substance is filled with a substantial visible matrix. The collagenous fibers embedded in the matrix are usually invisible. In contrast with areolar tissue, which contains much of the capillary bed, cartilage is avascular. It lacks lymphatic vessels and nerves. The dense fibrous connective tissue, forming **perichondrium** immediately surrounding cartilage everywhere except on articular surfaces, contains the vessels that supply oxygen and nourishment for its cells.

The principal form of cartilage is called **hyaline**, for its glassy appearance. Nearly all bones except the flat bones of the skull are at first cast in this material. How they become reconstructed and assume their per-

manent characteristics will be described in the latter part of this chapter. In the adult, only the articular surfaces of bones and the ends of the ribs

FIGURE 59. Developing hyaline cartilage from the nose of a cat fetus. Young chondroblasts are shown in the upper part of the illustration. 1200 ×.
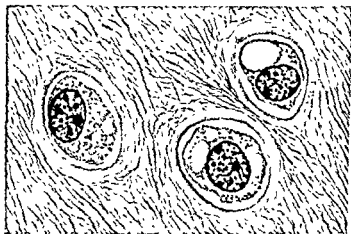
FIGURE 60. Hyaline cartilage from a rib of a monkey, showing the fibrillar structure of its matrix. 1200 ×.

(costal cartilages) remain cartilaginous. Hyaline cartilage likewise forms part of the nose, larynx, trachea, and bronchi of the adult. With advancing age, even some of these few cartilages tend to become calcified or ossified (Fig. 230), and their collagenous fibers become more prominent.

One of the earliest signs of aging is said to be transformation of hyaline cartilage into fibrous cartilage.

Cartilage develops from mesenchyme like other connective tissue. The mesenchymal cells multiply rapidly, withdraw their processes, and become crowded into masses, known as centers of chondrification. The more
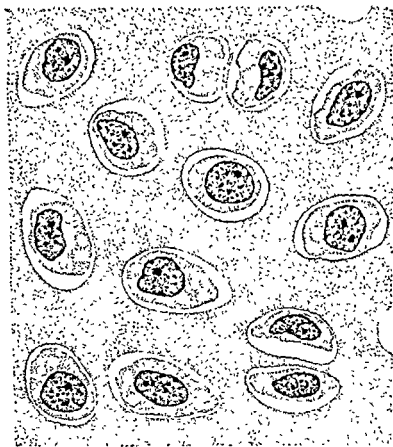
FIGURE 61 Hyaline cartilage in the femoral epiphysis of a puppy, showing chondrocytes shrunken away from their capsules. 1200 ×.

centrally placed cells increase in size, and vacuoles begin to appear in their cytoplasm At this early stage, they form **precartilage,** like the upper cells of Fig. 59. Interstitial matrix substance appears, at first staining with eosin; later, becoming dense and basophilic, it takes on its characteristic blue color with hematoxylin.

The collagenous fibers of hyaline cartilage cannot ordinarily be seen because they have a refractive index identical with that of the matrix in which they are embedded. Special techniques do show them, as illustrated in Fig 60. They are just as much a component of hyaline cartilage as of the other varieties. As the result of production of a compact matrix,

the cartilage cells become lodged in separate compartments known as **lacunae** (Fig. 61). The walls of lacunae of adult cartilage are more highly refractive than the surrounding matrix, stain intensely with basic dyes, and are said to form **capsules**. In the living condition, cartilage cells
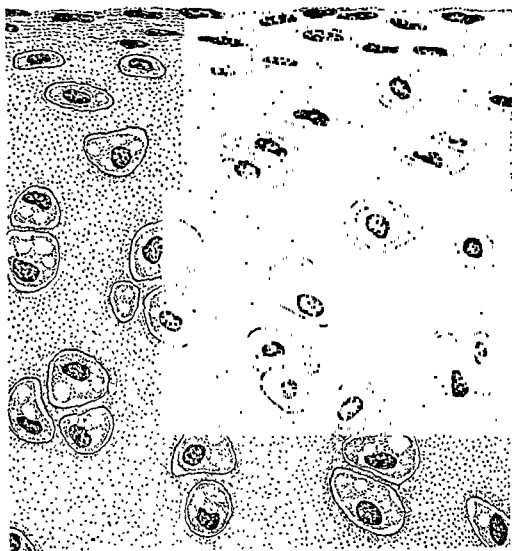
FIGURE 62 Hyaline cartilage of a monkey's trachea, showing the perichondrium (above), young chondrocytes, and older chondrocytes in groups 600 ×.

completely fill the lacunae, but in fixed and stained preparations you often see them shrunken away from the walls (Fig. 61).

Cartilage cells of the adult are *not evenly scattered* in the matrix, as they are in the fetus or the young individual. They tend to form groups arising through the repeated division of a single cartilage cell. Endogenous growth of cartilage occurs in this way. Exogenous or appositional growth takes place at the periphery of adult cartilage, where new cells

are added by multiplication and transformation of the cells of the peri-
chondrium. Figure 62 shows the gradual transition from fibroblasts or
primitive indifferent cells to cartilage. Recently divided cells of crescentic
shape separated by a thin film of hyaline matrix are often observed in
actively growing cartilage.

Thin slices of fresh cartilage demonstrate the general arrangement of
cells. Razor-thin sections can be examined in saline solution either with-
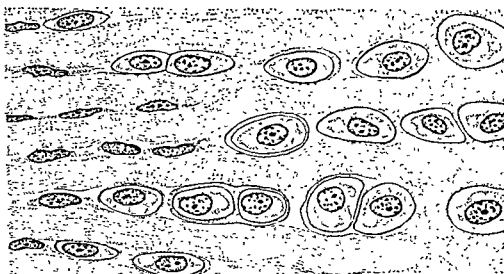
FIGURE 63 Junction of a tendon (left) with an articular cartilage (right) on
the humerus of a kitten, showing a form of fibrous cartilage in the middle transi-
tional zone 600 ×

out staining or after supravital staining. Fresh cartilage cells contain fat
droplets and glycogen granules. The presence of these substances is evi-
dence that cartilage cells are not starving, even though imprisoned in
their lacunae. Since cartilage is not supplied with capillaries, the fat and
glycogen, together with oxygen and other substances in solution, must
filter through the interstitial matrix to reach the cells. This occurs in ex-
actly the same manner as in the fluid-filled interstitial spaces of areolar
tissue.

The large masses of cartilage at the ends of long bones of the very
young prove too much for such filtration processes There, cartilage canals
made up of fibrous connective tissue containing blood vessels may extend
into the matrix to facilitate the penetration of metabolic materials

Besides hyaline cartilage, there are two other varieties of lesser promi-
nence. One is *fibrous cartilage,* which is actually a transitional form be-
tween hyaline cartilage and dense fibrous connective tissue of tendons

and ligaments. Its cells tend to line up in rows separated from each other by thick bundles of collagenous fibers (Fig. 63). The cells are usually spheroidal and are enclosed in capsules representing a condensation of the poorly developed hyaline matrix.

Fibrous cartilage in youth appears in the intervertebral discs and symphysis pubis, where a good many ligamentous bands are required to
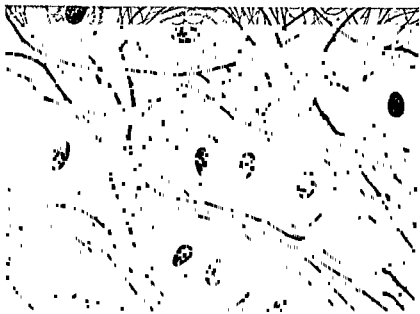
FIGURE 64. Elastic cartilage from a pig's ear, showing groups of hyaline cartilage cells and lacunae isolated by regions of connective tissue. Stained for elastic fibers. 600 ×.

unite the bones. Later it may be seen in tendons at their junction with bones and at places where tendons are subject to friction.

Elastic fibers may be added to the interstitial substance to form **elastic cartilage**. As in the fibrous variety, capsules of hyaline matrix and groups of cells are isolated by extensive fiber deposition. Besides the elastic network, collagenous fibers are present although inconspicuous. This variety, the least common one, occurs in the auricle of the ear, external auditory meatus, auditory tube, epiglottis, and in several minor cartilages of the larynx. It is illustrated in Fig. 64.

A small body of tissue bearing slight resemblance to degenerating cartilage is found in the center of the intervertebral disc, forming the **nucleus pulposus**. Its position corresponds to that of the notochord of the embryo, but it is probably not actually developed from that minute structure. Tumors resembling nucleus pulposus sometimes protrude into the vertebral canal and exert pressure upon the spinal cord.

BONE

Bone forms the skeleton of the body and is rarely found elsewhere. Its occurrence in certain tendons as nodules, the sesamoid bones, might be mentioned.[1] Its role in the construction of the skeleton is equaled or
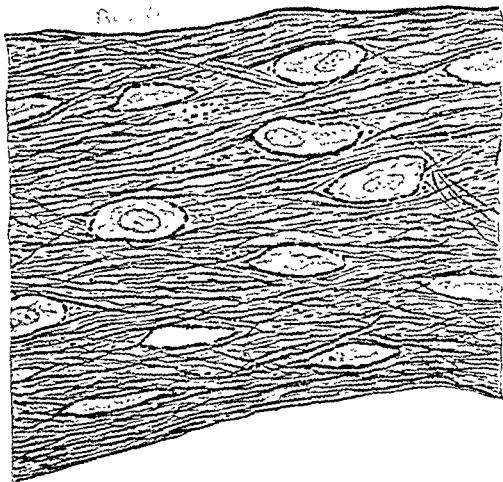
FIGURE 65 Bone trabeculum from a newly hatched cluck, showing its fibrillar structure Silver carbonate stain.

surpassed by the part it plays in storing calcium. More than 99 per cent of this essential element is found in the skeleton. You will need to revise any conception of bone you have gained by studying dry skeletons. Bone is fully as vital a tissue as blood.

Bone resembles cartilage in some respects. It, too, is a connective tissue made up of cells, interstitial matrix, and fibers. The matrix is most prominent, differing from that of cartilage by its heavy concentration of min-

[1] Other exceptions are the bone in the interventricular septum of the heart in large ungulates and the os penis in a number of mammals.
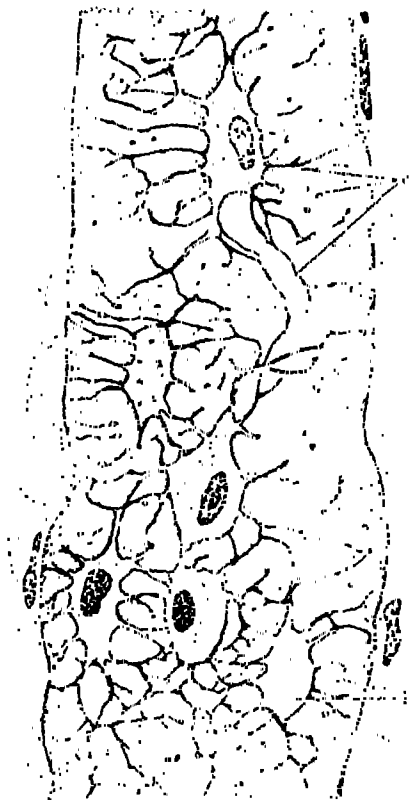
FIGURE 66 Bone trabeculum of a human femur, showing canaliculi, *c*, and osteocytes in lacunae, *l*. 1200 ×.

eral salts. As in hyaline cartilage, collagenous fibers form a strengthening framework, invisible in preparations by usual methods, but clearly shown in Fig. 65. Spaces called **lacunae** are occupied in life by **osteocytes.** These bone cells are not spheroidal like chondrocytes but extend many branching processes out into the matrix as illustrated in Fig. 66.

In most places, bone is closely invested by a dense fibrous connective-tissue sheath, the **periosteum**, which serves as a source of new bone cells for normal growth and repair. Along extensions of this connective tissue into bone canals courses a rich vascular supply.

Bone is constantly changing. You are aware of its growth throughout the early years of life, a phase that will be dealt with to some extent later in this chapter. Perhaps you do not realize that it undergoes atrophy with disuse and that hypertrophic bone changes occur with increased demand for support. Considerable molding can be effected surgically. The remarkable repair of seemingly hopelessly mangled bones attests to this. Its internal structure can undergo great modification, scarcely perceptible from the surface. As much as 60 per cent or more of the dry weight of bone is inorganic material, principally calcium phosphate.[2] The inorganic salts are not permanently bound in bone—far from it. When compounds containing radioactive calcium or phosphorus are administered to animals, radioactivity can be demonstrated in their bones within a few hours. Experiments of this type have shown that about one-third of the phosphorus in the skeleton of an adult rat is removed in three weeks. There is a continuous turnover of the inorganic constituents of bone, which are completely removed and replaced many times during life. Just as sodium and chlorine are banked in the interstitial fluid and matrix of fibrous connective tissue, so calcium and phosphorus are banked in the interstitial fluid and matrix of bone.

Living bone is not satisfactorily observed microscopically in the classroom, although it has been studied in tissue culture and in transplants into the anterior chamber of the eye. The student must content himself with stained sections cut from fixed decalcified bone and with tiny pieces of dry bone ground and polished until translucent. The latter type of preparation is highly instructive, although it goes without saying that cytological details are lacking.

In approaching the study of bone, it is well to start with a gross longitudinal section through the human femur. This will disclose the presence of two types of bony tissue: one, compact; the other, spongy. The two

[2] This is an oversimplification of the complex chemical structure of bone.

are continuous with one another and are actually different arrangements of the same histological elements. **Spongy bone** consists of a framework of anastomosing bars or **trabeculae** of various sizes and shapes. Their directions and points of contact are so arranged as to give each bone a maximum rigidity and resistance to changes in shape. The spaces among trabeculae are filled with marrow. All bone began as spongy bone. **Compact bone** occurs at and near the surface. In the larger long bones, the shaft or **diaphysis** consists of compact bone and has in its center a cavity filled with yellow marrow. The dilated extremities or **epiphyses** of long bones consist of spongy bone covered with a thin layer of compact bone. Compact bone is actually less dense than it appears, :or it is traversed by innumerable vascular channels.

In contrast with cartilage, 'one is richly supplied by 'ood vessels. The presence of freely anastomosing vessels influences the arrangement of bone cells and of the intercellular substance in which they are embedded. The blood supply of long bones is represented by a **nutrient artery** that is distributed directly to the marrow and by numerous smaller vessels arising from arteries of the periosteum. The periosteal vessels perforate the external layer of compact bone in small ' ' Volkmann **canals.** These commu─ ─   ' '   that run parallel   '   'one. These bear the name **Haversian canals.** Thus, an intercommunicating vascular bed is brought into close relationship with the interstitial substance of compact bone.

Compact bone in cross section, ground and polished: *c*, cementing line of Haversian system, *i*, interstitial lamellae. Compare with Fig. 67B. 300 ×.

In a thin polished piece of compact bone cut at right angles to the long axis, the Haversian canals look like black spots. They vary in diameter
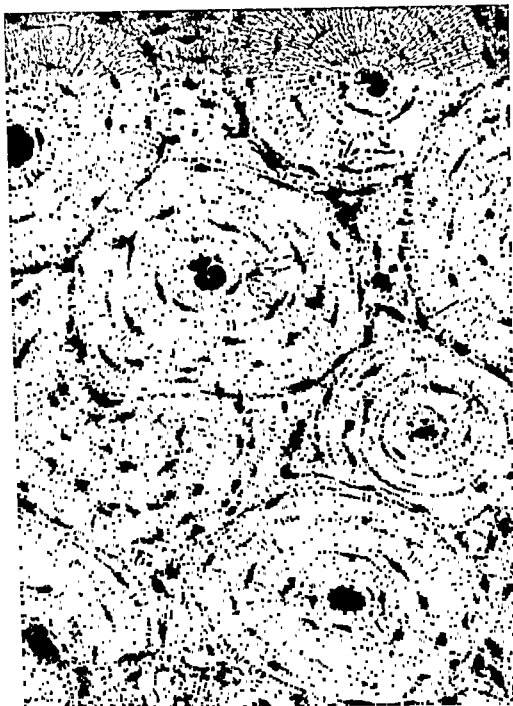
FIGURE 67B. Compact bone from the tarsus of a giraffe; a cross section, ground and polished. Parts of nine Haversian systems and seven canals will be seen The apparent overlapping is due to partial replacement of older by newer systems. Interstitial lamellae occur between the two upper Haversian systems Cementing lines appear as narrow bright bands at the periphery of some of the systems Specimen from the Piersol collection Photomicrograph, 300 ×.

but average roughly 50 μ. Around each of these canals is a variable number (4 to 20 or more) of thin plates or **lamellae** of matrix. Between lamellae are seen the little black holes or lacunae which contain the bone cells or **osteocytes** in life. These are rather evenly distributed. From each emerge many fine flagella-like canaliculi. Those nearest the Haversian canal open into it. More peripheral lacunae anastomose freely with each other through their canaliculi. The whole system of lamellae, lacunae, and canaliculi surrounding one Haversian canal is called a **Haversian system.** Forming the outer boundary of such a system and separating it from adjacent ones, a bright thin line, the **cementing line**, is often noticed. These details may be seen in Figs. 67A and B.

The bone between Haversian systems is arranged in parallel lamellae that have a definite orientation. They are known as **interstitial lamellae**, representing remnants of Haversian systems that were partly absorbed in the rebuilding process accompanying growth of bone (Figs. 67A and B).

The cortex, or most external layer of compact bone, consists of a series of thin concentrically arranged lamellae which are produced by the periosteum. These are circumferential or **periosteal lamellae**, which give a smooth appearance to the bone surface. A similar series of lamellae, fewer in number but also *concentrically* arranged, lines the wall of the marrow cavity. They are produced by the thin layer of fibrous connective tissue of the **endosteum** and are called **endosteal lamellae**. The periosteal lamellae are pierced by the Volkmann canals, which in life conduct blood vessels into the Haversian canals. The Volkmann canals are not surrounded by concentric lamellae.

In life, the bone cells fill lacunae and extend processes out into the canaliculi. Thus, they are shaped somewhat like fibroblasts (Figs. 65 and 66). Canaliculi anastomosing with adjacent ones provide a system of widespread but very minute channels throughout the matrix of bone. This permits tissue fluid to permeate through all parts of the bone substance, enabling osteocytes to live in a medium that is almost completely infiltrated with mineral salts.

Periosteum: A sheath enveloping the bone everywhere except over articular surfaces forms the periosteum, which consists of dense fibrous connective tissue. In its outer part run many blood vessels and some nerve fibers and lymphatics. Flattened connective-tissue cells occupy the inner part of the periosteum. These can give rise to the bone-forming cells, **osteoblasts**, under certain conditions. In a very young growing bone, osteoblasts are so numerous that they appear to form a special layer in

the periosteum. The capacity of periosteum to produce new bone is remarkable. If a large portion of the shaft of a long bone is shelled out from the periosteum, it may be replaced completely. In fractures, the periosteum contributes to the knitting together of the broken ends by laying down a **callus** of new bone.

The junction of periosteum and periosteal lamellae is marked in some places by visible collagenous fibers extending inward from the fibrous tissue of the periosteum. These are the **perforating fibers** that hold the periosteum firmly onto the bone. They are seen to best advantage at the sites where ligaments or tendons attach to bone. They may be compared with similar fibers in cartilage.

JOINTS

The histology of joints need occupy relatively little of your time, because it introduces no new tissues. The immovable or only partly movable **synarthroses** are characterized by dense fibrous connective tissue or cartilage between the bones. Sutures of the skull and intervertebral articulations represent two extremes. In sutures, the bones are held together tightly by perforating collagenous fibers. Dense fibrocartilaginous intervertebral discs and their surrounding ligaments unite the bodies of the vertebrae and permit a limited amount of movement.

In movable joints, or **diarthroses**, the ends of the bones are separated by a cavity containing some fluid. The articular surfaces are covered by a layer of cartilage—usually hyaline cartilage, although the fibrous form occurs in a few places. The outer surface of the articular cartilage lacks perichondrium and possesses rows of flattened chondrocytes. The deep cartilage is calcified. A dense fibrous connective-tissue **capsule**, ligamentous in nature, surrounds the joint and blends with the periosteum of the bones.

Within the ligamentous capsule is a layer of areolar tissue, often thrown into folds and projections which are the **synovial plicae** and villi. In some places, these are covered with cells resembling mesothelium. The **synovial membrane**, formed in this way, consists mainly of connective tissue containing a few fat cells. The connective tissue of the membrane becomes continuous with the perichondrium at the edges of the articular surfaces. Articular discs or plates of dense fibrous connective tissue or fibrous cartilage, continuous with the synovial membrane, project into the cavity between the bones of some of the large joints, like the knee

but average roughly 50 μ. Around each of these canals is a variable number (4 to 20 or more) of thin plates or **lamellae** of matrix. Between lamellae are seen the little black holes or lacunae which contain the bone cells or **osteocytes** in life. These are rather evenly distributed. From each emerge many fine flagella-like canaliculi. Those nearest the Haversian canal open into it. More peripheral lacunae anastomose freely with each other through their canaliculi. The whole system of lamellae, lacunae, and canaliculi surrounding one Haversian canal is called a **Haversian system.** Forming the outer boundary of such a system and separating it from adjacent ones, a bright thin line, the **cementing line,** is often noticed. These details may be seen in Figs. 67A and B.

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by a twofold process of construction and destruction. Unless you keep this always in mind, you cannot hope to understand the process of bone growth.

Before discussing development, growth, and reorganization of bone, it is well to know something about the cells that appear to have a good deal to do with these processes: the osteoblasts and the osteoclasts.
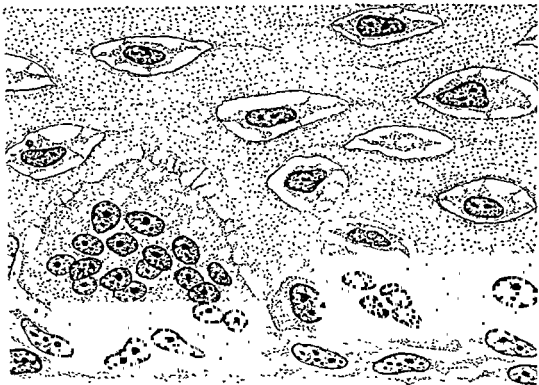
FIGURE 69 Osteoclasts, the large one in a Howship's lacuna, on a trabeculum of fetal jawbone. 1200 ×.

Osteoblasts develop originally by transformation of mesenchymal cells; later they arise by division of other osteoblasts and by transformation of indifferent cells of connective tissue. Osteoblasts look a little like plasma cells because they have dark eccentric nuclei, basophilic cytoplasm, and sometimes a washed-out region near the nucleus. They are easy to identify when they occur in single rows on the surface of growing bone. There they resemble low simple columnar epithelium (Fig. 68). Osteoblasts are associated with the deposition of new bone matrix in some manner not understood.

Osteoclasts are found in the region of bone resorption. The number present in an area may be taken roughly as an index of the rate of bone destruction. They are far less numerous than osteoblasts and are easily

The cavity of a joint may communicate with bursae outside of the joint. These are spaces lined with a continuation of the synovial membrane. The synovial fluid in the joint cavity and bursae is tissue fluid containing mucin, globulins, and proteins—substances imparting lubricating qualities to it. The movable joints are well supplied with blood vessels and lymphatic vessels. Nerve fibers and lamellated sensory corpuscles will be found in all diarthroses, for it is essential to keep you informed about the movements of your joints.

DEVELOPMENT, GROWTH, AND REMODELING OF BONE

At the time of birth, half of the centers of ossification have not appeared and less than one twenty-fifth of the bone of the adult has been

FIGURE 68 Intrame   ...ormation in the maxilla of a cat fetus Osteoblasts are aligned along a trabeculum of new bone. 1200 ×.

produced. Therefore, a consideration of development and growth of bone transcends the realm of embryology. Bone is increasing over a considerable fraction of the life span and, since it never completely loses its ability to undergo changes and repair, it is important to know how its growth and reconstruction take place. Bone is not simply piled on and on until adult size is reached. That might be the easiest procedure, but it certainly would not be the most economical one. Growth is accomplished

identified by their giant size (Fig. 69). They are the polykaryocytes mentioned on page 64. These multinucleated giant cells are often observed in little hollowed-out pockets in the bone. Such indentations are called Howship's lacunae.

FIGURE 71. Ossification in the terminal phalanx of a human infant's finger. A dark zone of calcifying cartilage borders the hyalin cartilage. Photomicrograph, 30 ×

The role of osteoclasts in bone destruction is not entirely clear. They do not phagocytize it, and instances of resorption in the absence of osteoclasts can be cited. Nevertheless, there is considerable evidence that they do assist in the process of tearing down existing bone.

The simplest picture of bone formation will be seen in studying **intramembranous ossification** of bones arising in embryonic connective tissue. The bones involved are the flat bones at the vault of the skull, the face, and the jaw. At fetal centers of ossification, numerous mesenchymal cells,
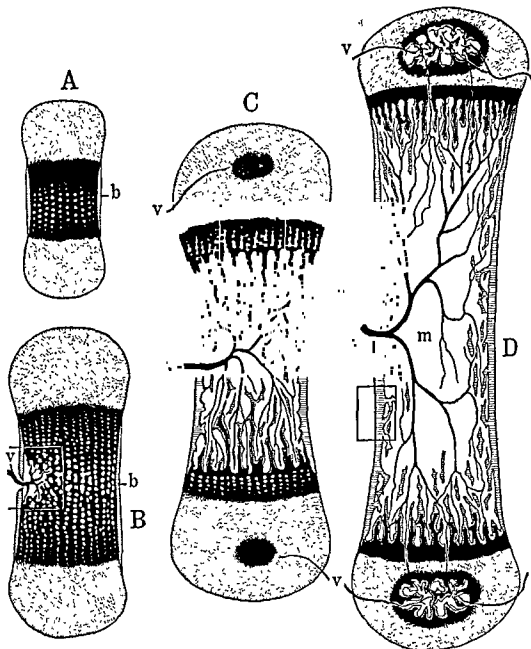
FIGURE 70. Diagrams of the ossification of a long bone: A, early cartilaginous stage; B, stage of eruption of the periosteal bone collar by an osteogenic bud of vessels, C, older stage with a primary marrow cavity and early centers of calcification in the epiphyseal cartilages, D, the condition shortly after birth with epiphyseal centers of ossification Calcified cartilage in all diagrams is black; b, periosteal bone collar; m, marrow cavity, p, periosteal bone, v, blood vessels entering the centers of ossification.

blood vessels. Later some of the mesenchymal cells become the myelogenous elements of bone marrow.

All the time bone is being built in the manner just described, the fetus is growing apace. Bones of the proper head or jaw size for one stage of

FIGURE 73 Diaphysis of a metacarpal bone of a cat fetus, showing penetration of vessels and osteogenic mesenchyme into calcified cartilage. b, periosteal bone collar, c, calcified cartilage; m, osteogenic mesenchyme, o, osteoblasts; v, blood vessels of an osteogenic bud. This figure corresponds to the area outlined in Fig. 70B. 600 ×.

development are quickly outgrown and must be redesigned from day to day. The osteoclasts play some part in the resorption that is a necessary step in the reconstruction of bone. Resorption in one place goes on simultaneously with production of new bone at an immediately adjacent one, so subtle is the transformation and so delicate the response to changing need.

While the membrane bones of the cranium are forming, a similar phenomenon occurs in the miniature cartilaginous models of the bones of the appendicular skeleton The process by which most of the cartilaginous

still loosely connected with each other by means of their processes, appear in a loose membrane of fine collagenous fibers, the **osteogenic fibers.** These cells are about to become osteoblasts. As they assume the characteristics of osteoblasts, they line up on fibers, and there appears along one side of the row of them some matrix substance which is the precursor of bone, although not yet containing lime. This is soon built into irregu-
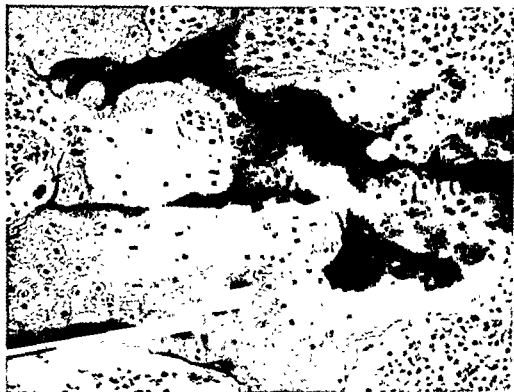
FIGURE 72. Trabeculum of bone, showing cores of darkly stained calcified cartilage. Same specimen as Fig 71. Photomicrograph, 300 ×.

lar bars (trabeculae) or slivers (spicules) with osteoblasts aligned on both sides. Shortly thereafter, the matrix begins to be infiltrated with calcium salts, and the first trabeculae and spicules of bone have been formed. This process goes out in all directions. Try to think of it in three dimensions.

The bars first laid down grow in thickness by deposition of new matrix at the osteoblast-matrix junction. Growth in length is accomplished by transformation of additional mesenchymal cells into osteoblasts, which appear in strands along the osteogenic fibers. As matrix is deposited, some of the osteoblasts lag behind and become imprisoned in the new bone by deposition of matrix all around them. Bone cells are formed in this way. The spaces between trabeculae contain mesenchyme and small

—exactly the same as in membrane bones. Figures 73 and 74 illustrate stages in development of periosteal bone.

While this goes on, or just preceding it, cartilage cells in the center of
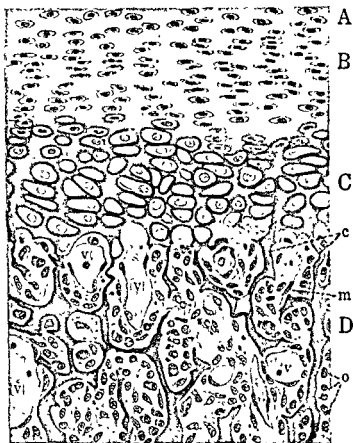
FIGURE 75 Endochondral bone formation in the ulna of a guinea pig fetus A, cartilage, B, zone of proliferating cartilage cells; C, zone of calcification of cartilage and hypertrophy of lacunae, D, zone of ossification; osteoblasts, o, appear on trabeculae of calcified cartilage, c, other cells of the osteogenic buds, m, may be seen, blood vessels, v, are present in the buds The region corresponds to that outlined in Fig 70C. 300 ×.

the bones begin to align themselves in longitudinal rows. Their lacunae enlarge (Figs. 70A and B). A corresponding decrease in intercellular matrix takes place. With continuation of this process, many lacunae merge to form irregularly elongated cavities, while remnants of the cartilage become calcified by infiltration with calcium salts. At the same time, embryonic connective tissue with blood vessels erodes the periosteal bone

skeleton is transformed into bone is known as **endochondral ossification**. It is illustrated diagrammatically in Fig. 70. For long bones, it begins at and around the center and proceeds in an orderly manner toward the ends until the definitive bone has been completed. A curious feature is
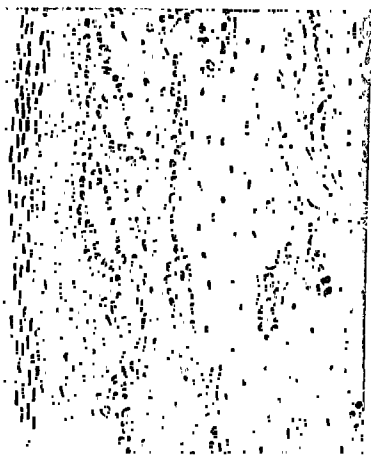
FIGURE 74. Periosteal bone in the humeral diaphysis of a 2-week-old kitten: *f*, young fibrous ligament lying on the surface of *v*, the vascular layer of periosteum, *o*, osteoblastic layer of periosteum This figure corresponds to the area outlined in Fig 70D 300 ×.

that bone formation never quite overtakes the growth of cartilage. In many bones of the body, more than a trace of cartilage remains on articular surfaces long after the process of ossification has been completed.

Endochondral ossification is accompanied by **periosteal bone formation** (Fig. 70). In long bones, this starts around the center of the shaft where a ring of osteoblasts forms in the fibrous perichondrium. This membrane is appropriately renamed periosteum as soon as the first matrix appears between osteoblasts and cartilage The process involves deposition of matrix on osteogenic fibers and its subsequent calcification

Muscular Tissue

Muscle is responsible for all the outward manifestations of life. Not only your movements, but also your heartbeat, breathing, and invisible activities of a visceral nature come about through muscular contraction. Contractility is the one fundamental property of protoplasm that most distinguishes animals from plants. It is present even in the lowest multicellular forms, where simple muscle-like cells produce movement.

Your own muscular tissue has more to do than provide motive power. Muscles serve to limit movements, brace against gravity, and maintain posture. They are constantly held in a state of partial contraction known as **tonus**. Thus they are always working, and by so doing they produce body heat. The dog's shivering comes about in response to a call for more heat.

The muscle of your heart is vital. Those of your other visceral organs play essential roles in respiration, digestion, excretion, and reproduction. Muscles of your blood vessels are extremely important for controlling blood flow and maintaining constant the internal environment of your protoplasm.

Muscular tissue exists only in combination with connective tissue, blood vessels, and nerves. Its elements are elongated cells, usually called **muscle fibers,** which have the ability to shorten and lengthen quickly. Three types of muscle fibers are regularly encountered in vertebrates: **smooth** or visceral, **skeletal** or somatic, and **cardiac** muscle. Their one common structural characteristic is the presence of fine **myofibrils** in their cytoplasm, giving them an appearance of faint longitudinal striation. Most muscle fibers occur in bundles or layers and, because of this, the full length of each individual fiber is impossible to see.

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collar and breaks into the cavities in the calcifying cartilage, forming **osteogenic buds** (Figs. 73 and 75), we say. These provide the cells that form osteoblasts and the osteogenic fibers on which to build bone. Then bone proceeds to form just as it does beneath the periosteum and in the embryonal skull membranes. The bits and slivers of the calcified cartilage that were left over after erosion of the cartilage matrix offer convenient foundations for deposition of bone matrix. Consequently you will encounter trabeculae of bone in the centers of which are deeply basophilic calcified cartilage remnants (Fig. 72).

The process of endochondral ossification extends toward the ends of the bones, preceded by rapid growth of the cartilage. Much later, after birth in almost all bones, secondary centers of ossification arise in the cartilage at the ends of the bone exactly as the primary ossification centers were formed (Figs. 70C and D). As this spreads out toward the oncoming primary ossification center, a band of cartilage marks the junction of diaphysis and epiphysis. This is the **epiphyseal cartilage**. Its continuing growth makes possible the lengthening of the bone. When ossification overtakes it after puberty, it is finally obliterated. The diaphysis and epiphysis fuse, and no further lengthening can occur. Throughout the course of growth, the bone increases in thickness by periosteal ossification. As growth in length and diameter proceeds, resorption and reconstruction take place to keep pace with the ever-changing needs.

Take up the human femur that you sawed longitudinally at the beginning of your study and, as you contemplate it, bear in mind that it was smaller than a paper safety match at the time ossification began in its center during the third fetal month.

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   Professor Clark's account of the structure and formation of bone is good. His descriptions of the factors involved in bone growth, times of formation of ossification centers, and vascularization of bone offer much information that was omitted in the present book. All is not histological but is most interesting.

2. Huggins, C.: The Composition of Bone and the Function of the Bone Cell, *Physiological Reviews*, vol. 17, pp. 119–143, 1937.
   This is largely a review of chemical aspects, but pages 132–136 deal with the bone cell.

short branching fibers have been seen in large arteries, such as the aorta (Fig. 76C).

Histological sections cut parallel to the long axis of smooth-muscle fibers reveal little about their structure. Figure 77 illustrates their appearance. Nuclei are seen as elongated bodies, and the whole layer of tissue
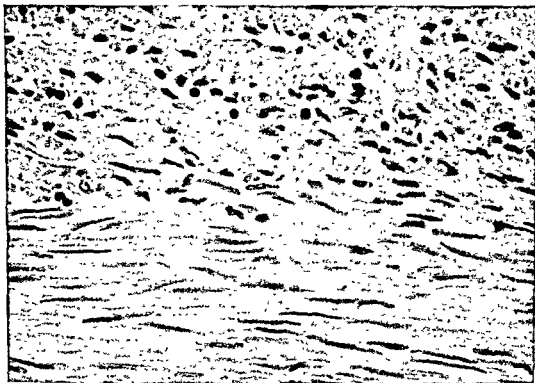
FIGURE 77. Smooth muscle of the human esophagus. Fibers are cut in cross section in the upper and in longitudinal section in the lower part of the figure Photomicrograph, 600 ×

has a longitudinally striated appearance. With hematoxylin and eosin staining, the fibrous connective tissue is more brightly pink than the cytoplasm of smooth muscle.

Cross sections show fibers of many sizes, depending on whether individual cells were cut in the middle or near the end. Since each cell has one nucleus and since it occurs in the middle, only the center section will reveal it. Furthermore, the nucleus may look large or small according to whether it was cut through its middle or through one of its tapering ends (Fig 77).

Smooth muscle is of widespread occurrence in the walls of tubular and hollow organs, where it forms layers or bundles. Its fibers are held to one

SMOOTH MUSCLE

Smooth-muscle fibers are the simplest of the three types. They are sometimes called **plain** because they are unadorned by the horizontal striations that characterize both skeletal and cardiac muscle fibers. Furthermore, they lack a distinct cell membrane. The cytoplasm of these long, thin, spindle-shaped cells has nothing very characteristic about its
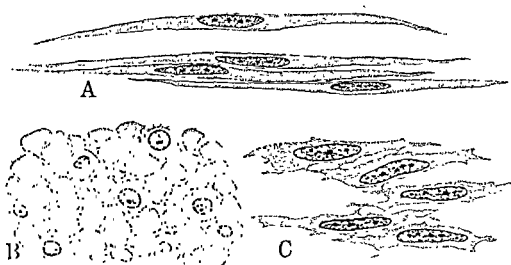
FIGURE 76. Smooth muscle: A, fibers isolated from a frog's bladder; B, cross section of fibers in the bladder of a kitten; C, branching smooth-muscle cells in the aorta of a dog. 900 ×.

appearance. The nucleus is cigar-shaped and lies in the center of the cell, one to each cell as a rule.

A good place to study smooth-muscle fibers is the wall of a hollow organ of one of the lower vertebrates whose cells are larger than those of mammals. Figure 76A illustrates a few isolated fibers from a frog's urinary bladder in a moderately contracted state. Nuclei appear longer and thinner in stretched fibers, and shorter and twisted or segmented in greatly contracted fibers. Twisted nuclei are sometimes seen in walls of blood vessels (Fig. 43).

Smooth-muscle fibers vary in length from 15 to 500 μ, depending on their location. Those of the intestine are about 200 μ long. The shortest occur in small blood vessels. Smooth-muscle fibers can increase greatly in size as the occasion demands. The lengthening is notable in the uterus during pregnancy where individual fibers become eight times their original size. They are unbranched in almost every location, although a few

been designated **myoepithelial** cells and are said to resemble the most primitive contractile elements in coelenterates. These are illustrated in salivary glands in Fig. 188 and in sweat glands in Fig. 175.

SKELETAL MUSCLE

Skeletal or somatic muscle forms the flesh of your body, constituting over 40 per cent of the total body weight and far exceeding any other

FIGURE 79 Developing skeletal muscle fibers, A, longitudinal section, B, cross section c, mesenchymal cells, m, myoblasts in several stages of development; y, young myoblast with four nuclei but no fibrils 900 ×.

tissue. Like other muscle and like connective tissue, it arises from mesoderm; more specifically, from that part of each mesodermal somite that is known as the myotome. Development begins in man about the sixth week and ends in most muscles before birth. Further growth consists of enlargement of the fibers.

Various stages of development can be seen side by side in fetal muscles, some of which are illustrated in Fig. 79 Closely packed cells of the myotomes become elongated and spindle-shaped The single nucleus initiates a series of divisions, producing multiple nuclei strewn along the axis of

another by some interstitial substance containing reticular fibers in fine
networks. These are well developed in the intestinal musculature and in
small and medium-sized arteries, as shown in Fig. 78. Individual muscle
fibers take up the least possible space in the layers, one spindle-shaped
cell overlying the neighboring cells, as shown in Fig. 76. The cells never
lie end to end.
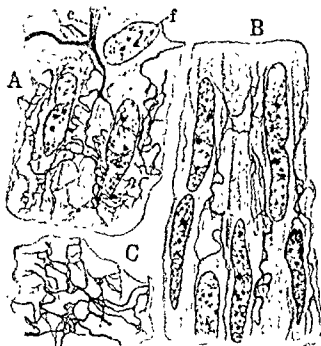
FIGURE 78. Smooth muscle in small arteries, A
and C, kitten's tongue, B, human kidney. c, col-
lagenous fiber; f, fibroblast nucleus. Reticular fi-
bers have been darkened by silver carbonate stain
900 ×.

Connective-tissue septa tend to subdivide the larger sheets or layers of
smooth muscle, providing ways for nerves and blood vessels to penetrate
them. Capillaries pass among smaller groups of fibers, but they are fewer
than in skeletal muscle.

Nerve endings of smooth muscle are quite simple (Fig. 133) and few.
Not every muscle fiber is innervated. In fact, most are not. Conduction is
readily effected over smooth-muscle fibers themselves. Contraction, en-
tirely involuntary, is slow and sustained, but can produce extraordinary
force; witness the uterus during labor. Smooth muscle does not become
fatigued so easily as the skeletal variety.

In a few restricted locations, such as the iris of the eye and certain
glands, cells of special nature occur among epithelial cells. They have

been designated **myoepithelial** cells and are said to resemble the most
primitive contractile elements in coelenterates. These are illustrated in
salivary glands in Fig. 188 and in sweat glands in Fig. 175.

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tomes become elongated and spindle-shaped The single nucleus initiates
a series of divisions, producing multiple nuclei strewn along the axis of

the growing myoblast. Meanwhile, myofibrils appear in the periphery of the cytoplasm. Later the nuclei come to lie at the periphery beneath the thickened cell membrane. Young muscle fibers can contract as soon as myofibrils appear.

Fibers of skeletal muscle are typically long, straight, unbranching[1] cylinders. They are cells, the largest in the body, varying between 10 and

FIGURE 80. Skeletal muscle of a cat's tongue, myofibrils are seen in cross section on the right, and in longitudinal section on the left. Iron hematoxylin stain. Preparation by the late Dr. George de Renyi. Photomicrograph, 900 ×.

100 μ in thickness and up to 4 cm in length (some claim 15 cm. or more). Some fibers of short muscles extend the entire length of the muscle. Most do not. The very active muscles, like those moving the eyes, have the thinnest fibers. The ponderous limb muscles have thick fibers.

The cell membrane of the skeletal muscle fiber is called the **sarcolemma**. Although it is a true cell membrane, it is so thick that it resembles the wall of a plant cell. It comes into close relationship at its nerve ending with the neurolemma, which is the cellular sheath of nerve fibers supplying the muscle fibers. It is tougher than the protoplasm of the

[1] In a few places, such as the attachments of some intrinsic tongue muscle fibers, branching fibers occur

muscle fibers, which can be fractured without tearing the sarcolemma by overstretching.

Skeletal-muscle fibers possess many nuclei—several hundred in the largest ones. The nuclei are ovoid and usually less elongated than those of
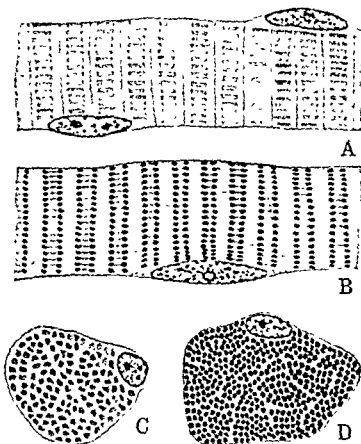
FIGURE 81. Skeletal-muscle fibers: *A* and *B*, longitudinal section; *C* and *D*, transverse section, somewhat diagrammatically represented. Compare with Fig. 80. The differences in appearance are due to variations in technical procedures.

smooth-muscle fibers. One of the two important features of a skeletal-muscle fiber is the peripheral location of its nuclei beneath the sarcolemma; the other is the crossed striations of the fiber.

Within the sarcolemma is the muscle cytoplasm, known as **sarcoplasm**. This is a viscous fluid containing myriads of **myofibrils**, 0.2 to 1 or 2 μ in thickness. In longitudinal sections, these fibrils are readily perceptible, but they are more easily seen in cross sections of well-preserved muscles. They impart a fine stippling to the cross section of fibers. This stippling

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may appear uneven because the fibrils tend to group together in columns, appearing in cross section as areas of dots in the more fluid cytoplasm (Figs. 80 and 81).

The **cross striations** of relaxed skeletal-muscle fibers are composites of
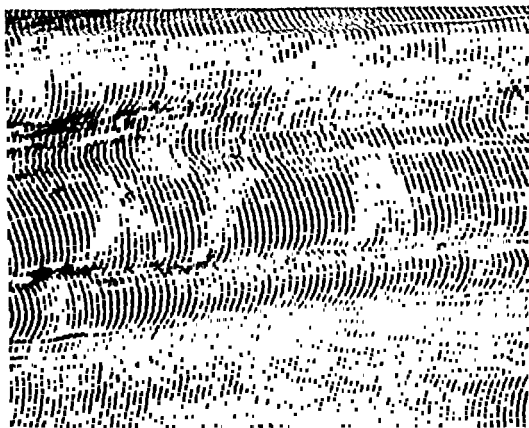
FIGURE 83. Bas-relief photomicrograph of human skeletal-muscle fibers in longitudinal section. This section is the same as Fig. 82B. 600 ×.

alternating light and dark portions of individual myofibrils. The light and dark stripes, known as **isotropic** and **anisotropic discs** when viewed in polarized light, are easily seen in any ordinary histological preparation (Fig. 82) but are demonstrated to best advantage with iron hematoxylin stain, which darkens the anistropic disc (Fig. 80). Well-fixed and stained longitudinal sections may exhibit an extraordinarily thin dark line transecting the isotropic disc. Rarely, a fine light line occurs in the anisotropic disc. These lines and the discs they traverse have been given some bothersome letter designations.[2] We know little, indeed, about the sig-

[2] The isotropic disc is called I by English and J by Germans, the anisotropic, A and Q. The dark line in the isotropic disc is Krause's membrane or Z, the light line in the anisotropic disc, Hensen's line or H. The portion of the fibril between two Z lines is a **sarcomere.**

FIGURE 82. Skeletal muscle from a man: *A* and *B*, cross and longitudinal sections. Photomicrograph, 600 ×.

trated in Fig. 86. These little vessels are the branches of slightly larger
vessels which run in the perimysial septa and surrounding connective tis-
tue, as shown in Fig. 84. The smallest capillaries course up and down
among the individual fibers, branching and anastomosing with each other.

Muscles are extensively innervated by motor and sensory nerve fibers.
Each muscle receives one **motor ending** (page 190). This does not mean
that each muscle fiber contracts individually. Numerous nerve endings on
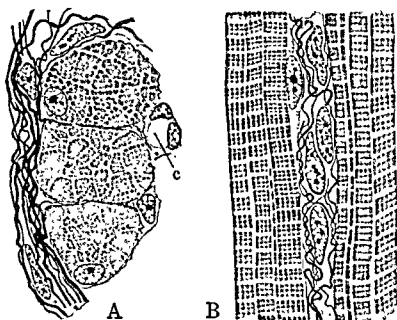
FIGURE 85. Skeletal-muscle fibers in a kitten's tongue, show-
ing reticular connective-tissue fibers of the endomysium, A and
B, cross and longitudinal sections: c, arterial precapillary. Silver
carbonate stain 900 ×.

numerous muscle fibers are associated with one nerve fiber. When a nerve
impulse comes down the fiber, the whole group of muscle fibers, con-
stituting a **motor unit**, goes into action together.

Sensory nerve fibers are supplied in a different way. In most muscles,
special groups of muscle fibers are set aside in connective-tissue sheaths:
these are the only ones from which messages may be received. They
do no real pulling. With their connective-tissue sheaths and nerve end-
ings, they constitute the **neuromuscular spindles**. These spindles are of
various sizes, consisting of 3 to 20 muscle fibers, each of which has the
usual motor nerve ending in addition to a sensory fiber termination (page
193). The spindle muscle fibers are usually shorter and thinner than the

nificance of the discs and lines, although theories are not lacking. For this, see more extensive books on histology.

A good deal of areolar connective tissue invests skeletal muscles, forming the fascia or **epimysium** surrounding them and the **perimysium** that
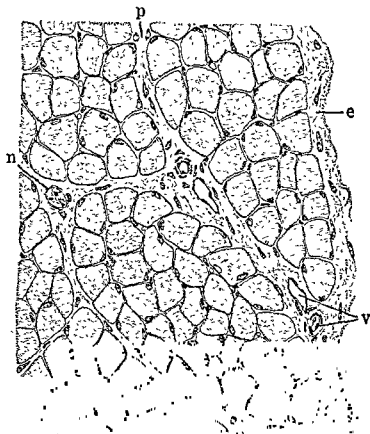
FIGURE 84. Skeletal-muscle fibres in a cat's gastroc-nemius muscle; *e*, epimysium; *n*, small nerve; *p*, peri-mysium, *v*, blood vessels. 300 ×.

subdivides them (Fig. 84). Individual muscle fibers are held together, and small bundles of them are set apart by delicate wisps of **endomysium**. The endomysium contains some reticular fibers (Fig. 85). The connective tissue serves to bring nerves and a rich blood-vessel plexus into close association with muscle fibers. Its fibroblasts and macrophages stand ready to repair extraordinary wear and tear of this active tissue.

Muscles are very well supplied with blood, as should be expected from the roles they play as prime movers of the body and generators of body heat. Portions of a capillary bed, stained by a silver method, are illus-

Nuclei of cardiac muscle look like those of skeletal muscle but occur in the interior of the fibers. Sarcoplasm is more abundant and lacks myofibrils in the vicinity of nuclei. The myofibrils are considerably coarser than in other types of muscle, and their tendency to group together in
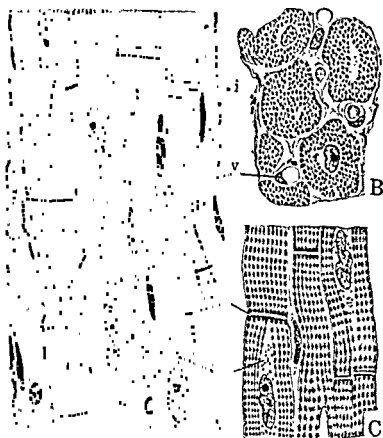
FIGURE 87. Cardiac-muscle fibers, *A* and *B*, ventricle of a monkey's heart, *C*, from a human heart *i*, intercalated discs, *p*, granules of pigment; *v*, blood capillaries Species and/or staining differences account for the variations in appearance of the intercalated discs. 900 ×.

columns is marked. They are present in living cells in tissue cultures. Their cross striations are like those of skeletal muscle. The sarcolemma is delicate and thin and is scarcely more than a light condensation of sarcoplasm. Transverse sections of cardiac-muscle fibers reveal details concerning the nature and distribution of fibrils and nuclei. It is instructive to compare them with similar sections of skeletal and smooth muscle (Figs 77, 82, and 88).

One of the most characteristic features of cardiac muscle is the presence of transverse bands, known as **intercalated discs** (Fig. 87). Each of

working fibers, and they taper. Nuclei may appear in the center of the fibers. Two spindles are shown in Fig. 136.

Muscle fibers end freely in the connective tissue within muscles or are

joined to dense connective-tissue fibers in fascia, periosteum, or tendons. At **myotendinal junctions**, the sarcoplasm is enclosed by the sarcolemma at the end of the muscle fiber, and the sarcolemma is firmly adherent to collagenous fibers of the tendon. Collagenous fiber bundles of the perimysial septa merge directly with the denser bundles of tendon fibers.
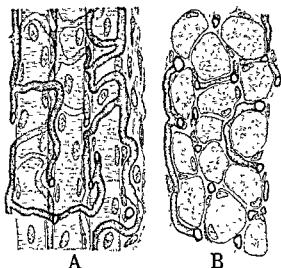
FIGURE 86. Capillaries surrounding skeletal muscle fibers in a dog's tongue, stained by a special silver technique: *A* and *B*, longitudinal and cross sections 300 ×.

CARDIAC MUSCLE

Cardiac muscle composes the heart walls and is found in the large veins entering it. There is considerable structural resemblance to skeletal muscle, although functionally it is more like the smooth variety. Its contractions are rapid, occurring rhythmically, tirelessly, and endlessly from a very early embryonal stage until death. The nervous system exerts some control over it, but it is not essential for inherent rhythmicity and plays no part at first. The nerves to cardiac muscle are similar to those of smooth muscle and are not at all like those of skeletal muscle.

The cells of cardiac muscle branch and anastomose with one another, forming a syncytium. Grossly they are arranged in layers or sheets that wind in overlapping spirals to form the myocardium. Sections through the ventricular wall of the heart will cut some fibers across and others lengthwise or obliquely. Figures 87 and 88 illustrate the appearance of this type of muscle.

Longitudinal sections through cardiac muscle will demonstrate branching and anastomosing muscle fibers, separated by delicate strands of loose connective tissue containing a rich capillary bed to keep this actively working muscle well supplied with blood (Fig. 87). This connective tissue contains many fine reticular fibers attaching to the sarcolemma of muscle cells.

these may extend completely across the fiber, running in a straight line or in a stair-step formation. The distribution of discs is irregular, although in favorably fixed and stained preparations it is less so. The intercalated discs seem to form boundaries between muscle cells, although this is
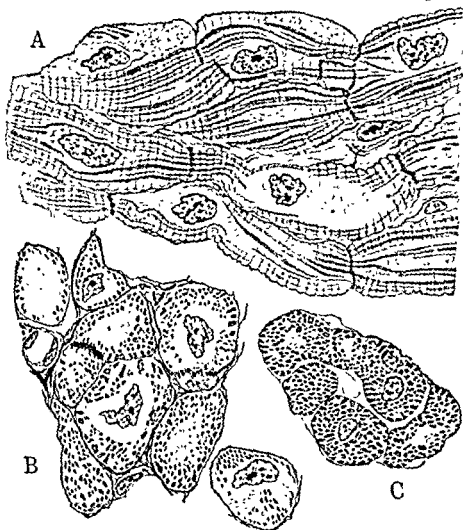
FIGURE 89. Purkinje fibers of the cardiac conduction system of a monkey. A, longitudinal section; B, cross section; C, ordinary muscle fibers for comparison. 900 ×.

really only a guess, for we know nothing about their purpose. They can be seen in living cardiac muscle grown in tissue culture.

Since rhythmical contractions of cardiac muscle are automatic and occur without direct action of the nervous system, conduction of synchronizing impulses takes place through the muscle tissue A special modification of cardiac-muscle fibers has been developed for this purpose. It is known as the **impulse-conducting system** of the heart and is com-
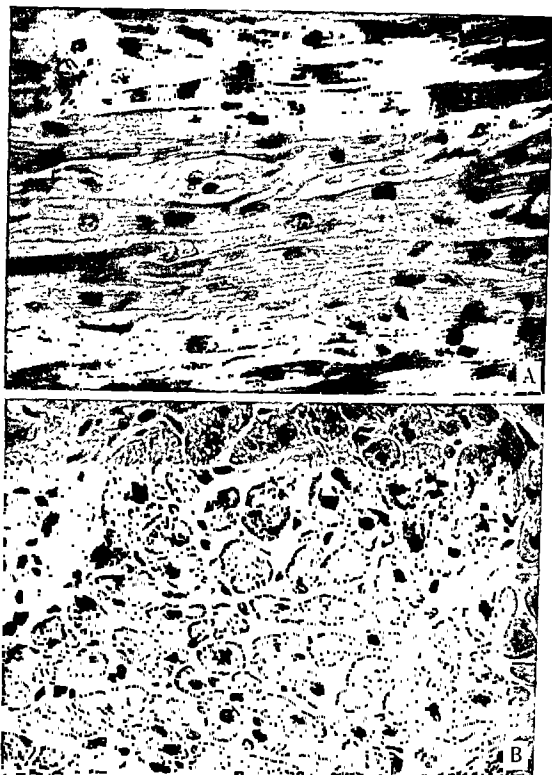
FIGURE 88 Cardiac muscle in a human heart ventricle: *A*, in longitudinal section, *B*, in cross section. Cross striations on the fibers are poorly stained, but central nuclei, intercalated discs, and branching fibers are seen. The epicardium is located at the upper left in *B* Photomicrograph, 600 ×.

Heart

The heart is really an overgrown blood vessel whose muscular wall has become highly differentiated for intermittent contraction. It has four chambers: two thin-walled **atria,** serving chiefly as reservoirs, and two thick-walled **ventricles,** which do most of the work. The atria receive the blood. The right admits the superior vena cava, the inferior vena cava, and the coronary sinus (vein). The left atrium receives the four pulmonary veins. Contraction of the muscular walls of the atria aids only slightly in passing blood on into the ventricles.

The ventricles act as a powerful double force pump which is most effective in sending blood on its way at just the right moment and with precisely the correct force into the pulmonary artery (right) and the aorta (left). The pressure required to force blood through the systemic circulation is much more than that needed to propel it through the lung. Correlatively, the musculature of the left ventricle is heavier than that of the right one.

FIBROUS SKELETON

Proper functioning of the heart depends on the presence of a skeleton of dense fibrous connective tissue which prevents overdistention of orifices and provides attachments for sheets of muscle. The atria are attached to the ventricles by a fibrous plate, the **atrioventricular septum.** Orifices in this septum are encircled by heavy fibrous rings, to the edges of which are anchored the flaps of the **tricuspid** (right) and the **mitral** (left) valves. Other orifices are associated with the pulmonary artery and aorta. Their **semilunar** valves attach to fibrous cuffs which also are part of the skeleton of the heart. Finally, the dense fibrous connective tissue extends into the septum between the ventricles.

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posed of special muscle fibers called **Purkinje fibers.** These differ from the working muscle fibers in a few particulars. Purkinje fibers are larger in ⋅diameter, appear swollen, and contain more sarcoplasm and relatively few myofibrils. Their nuclei look small and are centrally placed. They possess intercalated discs, just like those of other cardiac-muscle fibers. Figure 89 illustrates their appearance.

MUSCLE REPAIR AND REGENERATION

Of all varieties of muscle, cardiac is least able to undergo regeneration and repair. There is little evidence that its fibers can reproduce, but it is long-lived and remarkably resistant to daily wear and tear. Skeletal-muscle fibers can undergo some regeneration if the sarcolemma, a little of the sarcoplasm, and the nuclei are not entirely destroyed. But, again, it is questionable if whole new fibers can be formed from indifferent cells. Maintenance of skeletal muscle requires an intact motor nerve supply. Hypertrophy involves increase in fiber diameter, not increase in the number of fibers. Smooth-muscle cells are the least differentiated, and regeneration of them can take place. This occurs mainly from indifferent connective-tissue cells, although partly by mitotic division of existing muscles. Injuries and wounds are healed by connective-tissue scar formation in all types of muscle.

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   The relationship between muscle fibers and tendon and the role of argyrophil fibers is described in this article.

sions from these, the **papillary muscles**, give attachment to thin **chordae tendineae**, which fasten onto the free edges of the leaves of the tricuspid and mitral valves. These cords are made of fibrous connective tissue continuous with that of the endocardium, and they do not have any muscle in them.

The myocardium is permeated by loose fibrous connective tissue carry-

FIGURE 90. Endocardium of a human heart ventricle. Photomicrograph, 300 ×.

ing blood vessels and lymphatic vessels. The capillary bed is very extensive in cardiac muscle. Blood reaches it directly from the coronary arteries, which are the first branches given off by the aorta This blood, fresh from the lungs, gives up more oxygen in the capillary bed of the heart than does blood in any other organ. A rich lymphatic drainage can be demonstrated in the heart muscle.

The **epicardium**, or outer coat of the heart, is the visceral **pericardium**. It is formed by fibrous connective tissue covered with mesothelium. The branches of the coronary arteries, veins, and nerve plexuses course within it. Fat is found along the vessels. The main arteries of the heart anastomose freely with one another, but connections between vessels are inadequate to supply the heart muscle after sudden occlusion of one of the coronary artery branches. There are no end arteries The anastomoses in the capillary bed increase with age. Slow occlusion of a coronary artery

The two atria and ventricles are separated by **interatrial** and **interventricular** septa. The former is thin and partly *membranous* and presents a shallow depression, the **fossa ovalis**, which marks the site of the aperture by which *oxygenated inferior vena caval blood* from the placenta entered the left atrium during fetal life. The interventricular septum is thick and muscular except near the atrioventricular orifices, where it receives a strong extension of the cardiac skeleton, giving it the name **septum membranaceum**. This dense fibrous connective tissue is inelastic, contains a few cartilage-like cells, and has a tendency to calcify or even ossify in old age. The os cordis is found here in certain large mammals.

ENDOCARDIUM, MYOCARDIUM, AND EPICARDIUM

Three layers can be seen in the atrial as well as in the ventricular walls. The *innermost is the* **endocardium**, continuous with the internal coat of the vessels entering and leaving the heart. It is thicker in the atria than in the ventricles. Folds of it form valves, including the flaps that guard the inferior vena cava and the coronary sinus.

The innermost component of the endocardium is endothelium. Beneath this is a variable amount of fibrous connective tissue containing some elastic fibers and a few smooth-muscle cells. Blood vessels and branches of the special impulse-conducting system of Purkinje fibers course in the deeper layer of the endocardium. The structure of the endocardium is illustrated in Fig. 90.

The **myocardium** is the thickest of the three coats and is formed of cardiac muscle, which was described on pages 122 to 126. The atrial myocardium is thin. In the auricular appendages, it has ridges, called **pectinate muscles**, extending into the lumen. Its outer layer is common to both atria.

The ventricular myocardium is much more complex, and its arrangement can be studied to best advantage in gross specimens. There are no straight bundles running from the base to the apex of the heart. Instead, the sheets of cardiac muscle are spirally arranged, deep fibers encircling each ventricle, with the thickest construction in the left. The spiral arrangement of muscle bundles makes contraction peculiarly efficient. Each heart beat virtually wrings out the blood contained in the heart.

The internal surfaces of the ventricles are quite irregular, owing to projections of the myocardium which are called **trabeculae carneae**. These can be seen in the low-power photomicrograph in Fig. 91. Exten-

sions from these, the **papillary muscles**, give attachment to thin **chordae tendineae**, which fasten onto the free edges of the leaves of the tricuspid and mitral valves. These cords are made of fibrous connective tissue continuous with that of the endocardium, and they do not have any muscle in them.

The myocardium is permeated by loose fibrous connective tissue carry-

FIGURE 90. Endocardium of a human heart ventricle. Photomicrograph, 300 ×.

ing blood vessels and lymphatic vessels. The capillary bed is very extensive in cardiac muscle. Blood reaches it directly from the coronary arteries, which are the first branches given off by the aorta. This blood, fresh from the lungs, gives up more oxygen in the capillary bed of the heart than does blood in any other organ. A rich lymphatic drainage can be demonstrated in the heart muscle.

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may occur without disaster because these anastomoses provide a growing collateral circulation.

In certain places, the nerves form deep cardiac plexuses which contain
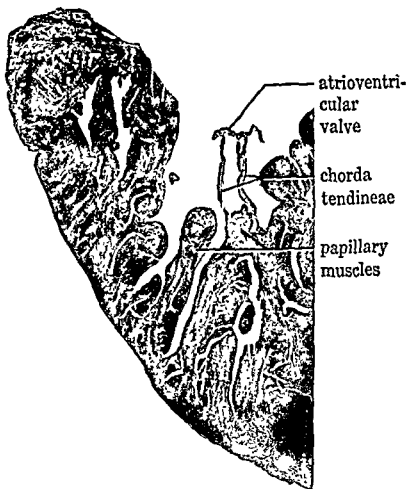
FIGURE 91. Ventricular myocardium of an infant's heart. Specimen in the Piersol collection. Photomicrograph, 4 ×.

autonomic ganglion cells. These lie in the epicardium and follow the course of the arterial distribution.

CARDIAC VALVES

The **cardiac valves** are all of similar structure. Since they are folds of endocardium, they are invested with endothelium, beneath which is dense fibrous connective tissue, continuous with that of the cardiac skeleton. The aortic and pulmonary valves have thin layers of elastic fibers on their ventricular sides. The atrioventricular valves are said to have a few smooth-muscle fibers on the atrial side. All are firmly anchored to the

fibrous rings or cuffs. The free edges of the valves are practically avascular. The comment has been made that no living tissue could withstand
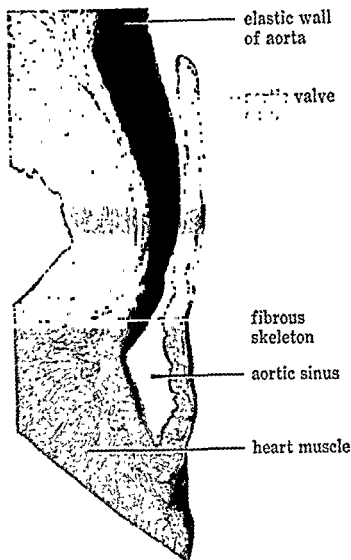
FIGURE 92. Aortic valve of a human heart. Stained for elastic fibers. Specimen in the Piersol collection. Photomicrograph, 8 ×.

the strain that has been placed on the heart valves. Although not strictly dead structures, the avascular valve edges are markedly fibrous. The structure of an aortic valve is illustrated in Fig 92.

IMPULSE-CONDUCTING SYSTEM

The impulse-conducting system of the heart is poorly understood from both structural and functional standpoints. It is constructed of the spe-

cial cardiac-muscle fibers (Purkinje fibers) arranged in strands beneath the endocardium.

The conduction system may be said to start at an accumulation of special cardiac muscle, nerve fibers, and connective tissue between the orifices of the superior and the inferior venae cavae. This is the **sinoatrial**, or **sinus node**. From it, fibers spread out into the atrial walls. Impulse-conducting tissue is concentrated also at an easily demonstrable **atrioventricular node** near the orifice of the coronary sinus. Thence, as the **atrioventricular bundle** (His), this tissue crosses the fibrous atrioventricular septum and divides into branches which spread out over the inner walls of the two ventricles.

The sinus node is called the pacemaker of the heart because it appears to initiate regulatory impulses for the contraction cycle of atria and ventricles. The conduction tissue is less easily seen in man than in certain other animals (Fig. 89), for the reason that its fibers are neither so distinctive in structure nor so completely isolated by connective tissue.

GREAT VESSELS

Cardiac muscle of the myocardium extends beyond the atrial walls onto the veins that enter them. A little of it may be encountered in the aorta and pulmonary arteries. Near the heart, the structure of all the great vessels is modified.

Both of the **venae cavae** have linings made up of endothelium and fibrous tissues, like the endocardium. They lack middle circular muscle coats, typical of most veins. Instead, they have a great deal of longitudinal smooth muscle and a variable amount of cardiac muscle in their outer coats. This serves to adjust their walls to tensions produced by the beating heart.

The **pulmonary veins** are relatively inelastic and possess a middle coat almost as thick as that of the branches of the pulmonary artery. Near the heart, it is formed very largely by cardiac muscle. Again, the internal coat is fibrous and thick like that within the atrium.

The **aorta** and **pulmonary artery** are elastic tubes surrounded by fibrous connective tissue as they leave the heart. The thick internal coat, continuous with the endocardium, contains elastic fibers. The muscle of the middle coat is more noticeable in infants and young individuals than it is in adults. But the main feature of these great arteries is the extensive

elastic-tissue development in the middle coat. Further description will be found in Chap. 10.[1]

REFERENCES

1. Patten, B. M.: The Heart and Pericardium, being part of Sec. VI, pp. 583–606, in *Morris' Human Anatomy*, 10th ed. rev., J. P. Schaeffer, editor; Philadelphia, The Blakiston Company, 1947.
   Read the first thirteen pages of this descriptive account, which is one of the best It is fundamental for any knowledge of the intrinsic structure.

2. Windle, W. F.· The Fetal Circulation, being Chap. 3, pp. 29–48, in *Physiology of the Fetus*; Philadelphia, W. B. Saunders Company, 1940.
   This is a brief description of the important changes that take place in the heart at birth.

[1] See Visual Aids, 15 and 16.

Blood Vessels and Lymphatics

The systems of tubes of various sizes that carry blood from the heart through the tissues and back to the heart again and the thin channels that convey lymph from the tissues to the heart should now engage your attention. You cannot well avoid observing the blood vessels; in fact, you have already encountered them many times. You may not have seen the lymphatics, for they are more obscure than arteries and veins. Almost everywhere in the body, these blood and lymph vessels course in fibrous connective tissue. Conduction of vessels is one of the functions of connective tissue. Not all parts of the body are supplied by lymphatics nor, for that matter, by blood vessels, although no living tissue component gets very far away from a blood supply.

Blood vessels, except the very smallest, are always full of blood in the living body, but many of those you will see in histological preparations are empty. This, you must remember, is a most unnatural condition. Blood-vessel walls, especially arterial walls, have great elasticity and contract when the heart stops beating. Figure 93 shows small blood and lymphatic vessels that have not collapsed at the time of death and fixation of the tissues.

The largest blood vessels are constructed for the purpose of conducting blood. Those of intermediate size have taken on an additional duty, that of regulating blood flow and distribution. The smallest vessels are the vital ones. From them, the materials carried by the blood can get into the tissue fluid. They are the capillaries.

CAPILLARIES[1]

Capillaries are simple endothelium-lined tubes connecting arteries with veins. All vessels, and even the heart, begin in the embryo as capillaries,

[1] See Visual Aids, 9, 10, 16, and 21

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adding layers of connective tissue and muscle as they develop. Capillaries are always small. They are about the size of a red blood corpuscle or a
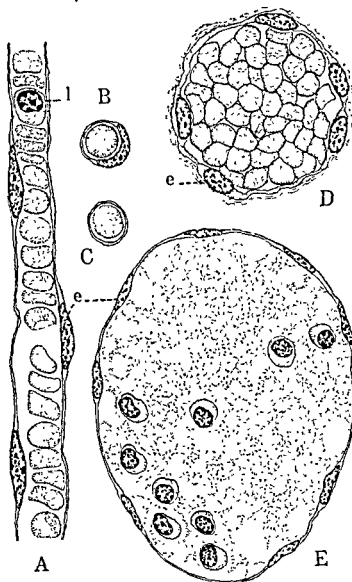
FIGURE 93 Small blood vessels and a lymphatic vessel, as they appear in histological sections. A, capillary in longitudinal section, B and C, in cross section, red corpuscles and a lymphocyte, l, in their lumens, D, small venule, containing red corpuscles; E, lymphatic capillary with lymphocytes and coagulated lymph in its lumen Endothelial nuclei are indicated at e 900 ×.

little wider, measuring 8 to 10 μ in diameter. This is illustrated in Figs. 93A, B, and C.

Density of the capillary bed is variable in different tissues. It increases

or decreases from time to time in an organ according to degree of activity of the organ. The number of capillaries actually conducting blood at any time is inconstant, especially in organs that alternate periods of
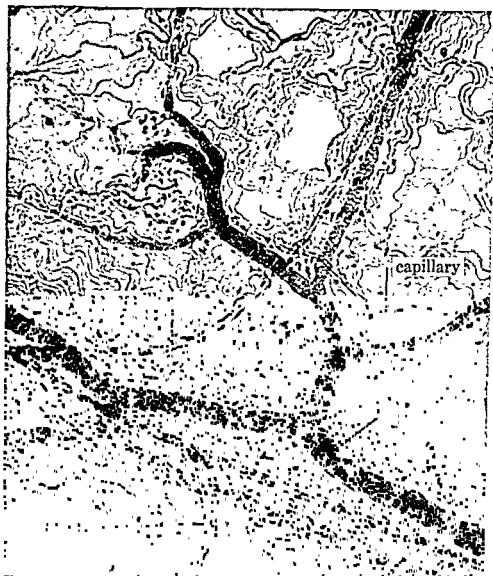
FIGURE 94 Small blood vessels in the human mesentery, spread upon a slide and stained with carmine. Photomicrograph, 150 ×.

work with periods of rest. In muscle at rest, most capillaries are closed, but after strenuous exercise, the number of open capillaries may increase as much as fiftyfold. Were all your capillaries open all the time, there would be little blood to fill your heart and you would die.

The total area of capillary walls in skeletal muscle has been estimated at about 6,000 sq. meters. Furthermore, each cubic centimeter of blood

flowing through muscle makes contact with about 6,000 sq. cm. of capillary wall. That is where diffusion of dissolved substances into the tissue fluid takes place. The appearance of a small portion of the capillary bed in the mesentery is shown in Fig. 94.

The capillary wall presents a smooth inner surface paved with endothelial cells, held to one another with a little interstitial cementing substance. Leucocytes can crawl into the tissues through this substance. Here, too, leakage of red blood corpuscles can take place abnormally. But remember, there are no holes in healthy capillaries. Diffusion of fluid and chemical substances is through a membrane. The interstitial substance, blackened with silver, appears as in Fig. 19B. The cells have ovoid nuclei which stain rather pale with hematoxylin and resemble nuclei of fibroblasts. Actually, the endothelial cells and fibroblasts are very closely related.

Sections through capillaries may cut a nucleus, which produces a bulge in the lining (Fig. 93A and B). This makes them easy to identify. When not sectioned through a nucleus, especially when they are collapsed and have no blood corpuscles in them, it is usually impossible to distinguish all the capillaries in a histological section.

Loose fibrous connective tissue containing tissue fluid is found around capillaries. The cells around capillaries are the usual connective-tissue cells: fibroblasts and macrophages. No muscle or other contractile cells clasp them.[2] Capillaries do not contract actively of their own accord and have no motor nerve supply. Slightly larger vessels, precapillaries, on the arterial side of the capillary bed do have a few smooth-muscle cells in their walls, and they can contract to regulate the flow of blood into the true capillaries. The capillary wall is living protoplasm and will exhibit some local contractility if probed by a micromanipulator needle, but that does not indicate active contractility.[3]

The capillary connections between arteries and veins in the spleen, liver, bone marrow, and some endocrine glands are wide channels, up to $30\,\mu$ and more in diameter. In these sinusoids, blood flow is very sluggish, and there is ample opportunity for macrophages clinging to their walls to phagocytize materials in the blood.

[2] Cells of Rouget on capillaries of the frog's nictitating membrane are said to contract actively, but this is questioned.

[3] See Visual Aids, 10 and 21.

PRECAPILLARIES

The concept of the **arterial precapillary** is important because those who hold that capillaries contract are referring to this type of vessel. The arterial precapillary is the contracting capillary-like vessel between the smallest arteries and the true capillaries. The anatomist calls it an artery because its wall contains a few smooth-muscle cells. Some physiologists call it a capillary because it is scarcely larger than the smallest true capillary. In the living animal, it is very difficult to observe its muscular coat, which consists of only an occasional smooth-muscle cell.

A **venous precapillary** has been described by some authors, just to make the series complete. It is nothing more than a big capillary about to join a venule.

MUSCULAR ARTERIES

All arteries big enough to be seen without magnification have walls consisting of three coats: The internal, or **tunica intima**, is the endothelial lining with some connective tissue beneath it. The middle coat, or **tunica media**, is formed by smooth-muscle and connective tissue, principally elastic, arranged mostly in circular fashion. The external coat, or **tunica adventitia**, is fibrous connective tissue with various other things in it, principally arranged longitudinally. The three coats are usually delimited by **elastic membranes**, internal and external.

Muscular arteries are sometimes called distributing arteries. They can regulate blood flow to different regions by contraction and relaxation of smooth muscles in their walls. They vary in size from vessels as big as the brachial or femoral arteries to those so small that they bear no specific name. Although all adhere to the general plan just outlined, there is considerable variation to meet particular needs. One of the characteristics of muscular arteries is the ability to grow in size when the occasion demands. When circulation to a region is impaired by occlusion of the main arteries supplying it, smaller collateral arteries take over and increase in size to carry the necessary volume of blood. Another important protective characteristic is the ability to contract spastically when injured and thus prevent fatal hemorrhage.

Arterioles: The very smallest arteries, **arterioles**, are members of the muscular artery class. They are the guardians of the capillary bed. The circular smooth muscle in their tunica media is extraordinarily sensitive

FIGURE 95. Venules, *v*, and arterioles, *a*, in subcutaneous tissue; fat cells, *f*. Photomicrograph, 600 ×.

to calls for more or less blood. Motion pictures of their activities are better than descriptions.[4]

The tunica intima consists of endothelium and an internal elastic mem-

[4] See Visual Aids.

brane, which may be incomplete in the smallest arterioles. In cross sections, the membrane appears as a corrugated, highly refractive line throwing the endothelium into folds which bulge into the lumen (Fig. 43). The adventitia is about one-third or one-fourth as thick as the muscular coat and merges with surrounding connective tissue. It is ill defined in
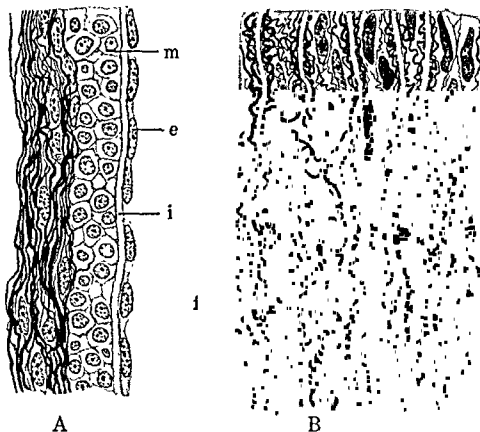
FIGURE 96. Reticular fibers in arterial walls, A, in the adventitia of a small muscular artery (longitudinal section) of the tongue of a kitten, B, in the media of the human aorta: e, endothelium; f, elastic plate of the aorta; i, internal elastic membrane, r, fine reticular fibers; m, muscle nucleus. 600 ×.

the smallest arterioles, in which the muscular coat consists of only two or three layers of short muscle fibers. Although a few elastic fibers appear in the wall of the arteriole, no external elastic membrane can be seen. The smallest arterioles merge with precapillaries and capillaries. The upper size limit is arbitrarily defined as 0.5 mm. Examples of arterioles are to be seen in Fig. 95 and in other illustrations in this book.

Muscular arteries of larger size. The large and medium-sized **muscular arteries** have delicate connective tissue in a subendothelial layer of the tunica intima. The internal elastic membrane is a well-developed fenes-
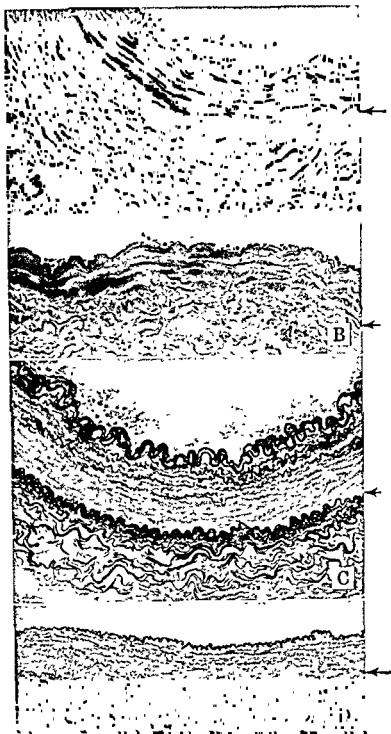
FIGURE 97. Intercostal artery and vein. *A* and *B*, hematoxylin stain; *C* and *D*, stained for elastic fibers Arrows mark the boundaries between muscularis and adventitia. Photomicrographs, 130 ×.
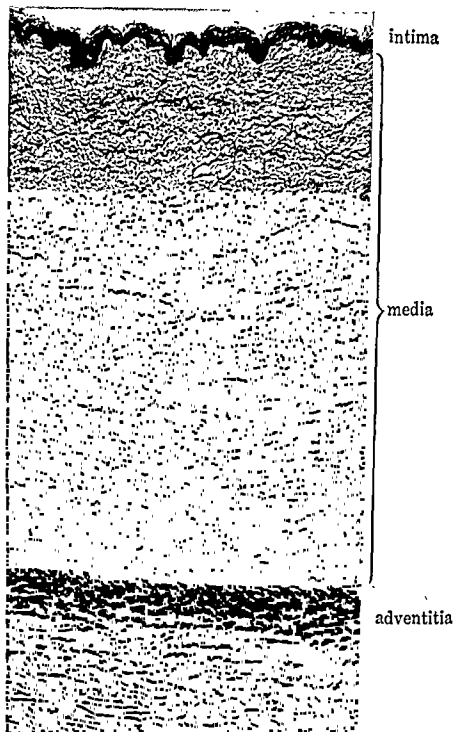
FIGURE 98 Femoral artery of a man, stained for elastic fibers. Compare with the femoral vein in Fig 102. Photomicrograph, 130 ×.

trated membrane. A few special arteries contain some longitudinal smooth-muscle fibers in the tunica intima.

The muscle fibers of the tunica media are spirally arranged and may

form 20 to 40 layers, more in the arteries of the lower extremity than in the upper. Elastic fibers are interspersed among muscle fibers. Some reticular fibers also are demonstrable (Fig. 96). The muscle fibers predominate in the smaller muscular arteries, but the elastic fibers crowd in
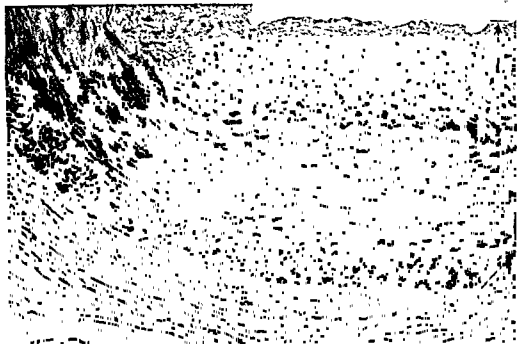
FIGURE 99 Human coronary artery, showing thick intima, i, and extra longitudinal smooth muscle at τ, outside the media, m Photomicrograph, 130 $\times$.

among them in the larger vessels, like the external iliac arteries, so that no sharp line of demarcation exists between typically muscular and typically elastic arteries.

The tunica adventitia may be as thick as the tunica media. Elastic fibers occur next to the media in coarse networks which condense to form the external elastic membrane. The fibrous connective tissue has a longitudinal orientation, predominantly, and when smooth muscle occurs in the adventitia, its fibers are arranged longitudinally. The structure characteristic of small muscular arteries is shown in Figs 97A and C. A large muscular artery may be seen in Fig. 98.

Muscular arteries, especially the larger ones, require a blood supply of their own. Consequently, **vasa vasorum** are encountered in the adventitia. These are arterioles distributing blood to capillary beds in the tunica media.

There are **variations among the muscular arteries**, not only in size but also in amount and distribution of elastic, collagenous, and muscle

fibers in the walls. The cerebral arteries are thin and look like veins. They have little elastic tissue except in the internal membrane and show only a meager adventitia. The branches of the pulmonary arteries also are thin-walled vessels with little elastic tissue.

On the other hand, the coronary artery walls are thick and have much elastic tissue, even an extra fenestrated elastic membrane, in the tunica media. A heavy tunica intima is commonly present. Longitudinal smooth muscle is sometimes found in the intima. A heavy outer longitudinal or spiral layer of muscle may be present, as may be seen in Fig. 99. Even at birth, coronary arteries of males are said to have thicker intima than those of females.

At puberty the arteries of the penis undergo development of the intima and media, with longitudinal muscle appearing in the thickened intima. Similarly, bands of longitudinal muscle occur in the intima of the uterine coiled arteries. The renal arteries exhibit an unusual amount of elastic tissue for their size. Arteries that are tortuous, like the splenic, and the large branches of elastic arteries are apt to develop longitudinal smooth muscle in the tunica adventitia.

ELASTIC ARTERIES

Elastic arteries are the large vessels that conduct blood by the shortest possible route to the distributing vessels. They are deeply placed and protected. This is well, as they cannot constrict to obstruct and obliterate their lumens when severed. Besides the aorta and pulmonary arteries, other elastic arteries are the innominate, common carotid, subclavian, and common iliac arteries. All resemble the aorta, but the smaller members of the group possess more smooth muscle and fewer elastic membranes. In branching to form smaller vessels, the structure changes gradually to that of the muscular type. The only great conducting artery that is nonelastic is the highly muscular ductus arteriosus between the pulmonary artery and the aorta. That is disposed of in short order at birth when it contracts and becomes permanently obliterated.

The tunica intima of the elastic arteries consists of the usual endothelium, with subendothelial tissue. It is thicker than in muscular arteries (less so in youth than in old age) and contains networks of elastic fibers as well as fenestrated elastic membranes. Usually there is no one distinct internal elastic membrane, but the several fenestrated membranes merge with those of the tunica media.

The tunica media contains smooth-muscle fibers, mostly circular but some longitudinal. However, the muscle is inconspicuous because its
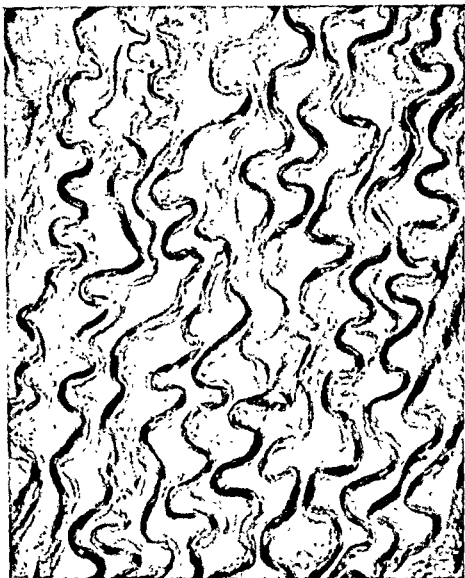
FIGURE 100. Fenestrated elastic membranes in the aorta of a female lion cub; stained for elastic fibers. Specimen in the Piersol collection Photomicrograph, 600 ×.

cells are crowded apart by many fenestrated membranes and elastic networks. There may be as many as 65 of these in the arch of the aorta. Sections stained with orcein and other special elastic-fiber stains reveal the membranes to the best advantage (Fig. 100), but the membranes are clearly visible in ordinary preparations because of their size and high
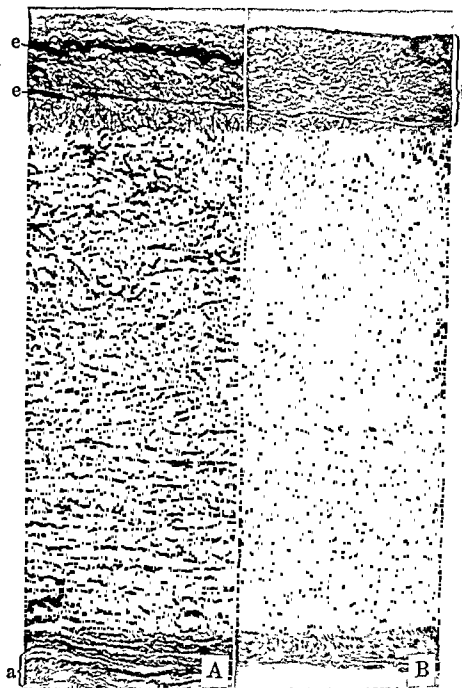
FIGURE 101. Aorta of a man, in longitudinal section: *A*, stained for elastic fibers, *B*, the same preparation with hematoxylin stain. The intimal layer, *ι*, contains two prominent elastic membranes, *e*; a small part of the adventitia, *a*, is shown in *A*; the rest of the wall is media. Photomicrographs, 130 ×.

refractive index. Compare Figs. 101A and B. Networks of reticular fibers occur among other elements of the tunica media.

The tunica adventitia of the elastic arteries is relatively thin. It is tough and serves a good purpose in limiting the amount of dilatation of the tunica media. It is made up of collagenous fibers arranged in long, loose spirals. Among these are small blood vessels, the vasa vasorum. The adventitia merges with surrounding loose fibrous connective tissue.

The walls of elastic arteries are much thinner in relation to size of lumen than are those of muscular arteries. By virtue of their great elasticity, they act as shock absorbers or compression chambers, smoothing out the flow of blood by dilating passively with each systole and resuming their original diameter during diastole of the heart. Were it not for their elastic construction, blood would move intermittently, instead of continuously, through the small vascular channels. As a matter of fact, in extreme degrees of sclerosis[6] of elastic arteries, the pulse can be observed in capillaries, although it is never visible there normally.

VEINS

Veins are the comparatively thin-walled tubes that conduct blood from the capillary bed back to the heart. Because the returning blood flows more slowly and is under less pressure than in the arteries, the lumen of veins is greater and the amount of elastic tissue in their walls is reduced. Veins do not adhere closely to the general blood-vessel plan. Some depart markedly from it. Since most are simply conducting tubes, they are formed principally by fibrous connective tissue. The reduced blood pressure calls for no strong fenestrated elastic membranes. A throttling and distributing mechanism is undesirable in most veins. Correlatively, there is little circular smooth muscle. In many places there is none.

Special mechanisms develop in veins, aiding the return of blood to the heart. These are valves and longitudinal bands of smooth muscle, most prominent where the force of gravity is to be overcome.

Venules: Little veins are called **venules.** The smallest ones look much like large capillaries, but their walls have some fibrous connective tissue forming a thin layer outside the endothelium. They function like capillaries and permit diffusion into the surrounding tissue fluid. Venules 40 to 50 μ in diameter have a few isolated smooth-muscle cells wrapped circularly about them. A complete vascular tunica is absent in venules

6 Degenerative replacement of elastic by inelastic fibrous tissue.

smaller than 0.2 mm. in diameter. Little veins of this size have relatively thick adventitial coats.

Veins of medium and large size: Medium-sized veins usually course with muscular arteries. They vary structurally in different locations. A tunica intima is thin in the smaller members of this group (Fig. 97) and, although elastic fibers can be demonstrated, a true internal elastic membrane is lacking as a rule. It is difficult to see a clear division between

FIGURE 102. Human femoral vein: stained for elastic fibers. The approximate junction of media and adventitia is 15 mm. below the lumen. Photomicrograph, 130 ×.

tunica intima and media in most veins. The femoral vein is shown in Fig. 102.

Valves occur as folds of the tunica intima in most veins as large as 2 mm. in diameter or more which are conducting blood against the force of gravity. They are absent in some of the visceral veins and in all those of the brain, spinal cord, and meninges. They are illustrated in Fig. 218.

The tunica media of veins is thin in contrast with that of accompanying arteries (Figs. 98 and 102). It may be absent altogether. It consists of circularly arranged smooth-muscle fibers with some fibrous connective tissue, but the number of elastic fibers is small. Veins of the lower extremities, pulmonary veins, and the veins of the gravid uterus exhibit a well-developed layer of smooth muscle in the tunica media. Veins of the cranium, the retina, the bones, and those of the deep layers of the maternal placenta have no muscle at all. The tunica media is missing in the

FIGURE 103 Inferior vena cava of a man, abdominal
portion: circular smooth muscle may be seen at the ar-
row; the rest of the wall is made up of connective tissue
and longitudinal bundles of smooth muscle Preparation
by Mr. James Rankin. Photomicrograph, 130 ×.

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mechanisms to aid in regulating peripheral blood flow and decreasing peripheral resistance.[6]

Most **arteriovenous anastomoses** are located in the skin of exposed parts of the body and in the walls of the intestinal tract, where they serve to reduce blood flow through the mucous membrane when digestion is not in progress. In the skin, they are prevalent in the nose, lips, finger tips, and toes, but especially in the nail beds. The cavernous spaces of erectile tissue are a type of arteriovenous anastomosis.

A highly developed arteriovenous anastomosis is illustrated in the **coccygeal body** (Fig. 104). This consists of a group of anastomoses arranged in a mass of dense fibrous connective tissue. The walls of anastomosing vessels are thick and muscular to make possible a complete occlusion when not needed. The smooth-muscle cells are short and somewhat hypertrophied. They are abundantly supplied with motor nerve fibers, and some sensory endings occur among them.

CAROTID BODIES

The **carotid body** is a small glomus at the bifurcation of the common carotid arteries resembling the coccygeal body. It is not an arteriovenous anastomosis but is a series of irregular cords of epithelioid cells closely associated with wide capillaries, which receive blood from a small branch of the carotid artery. A rich sensory nerve supply is provided by a branch of the glossopharyngeal nerve. The carotid body is a chemoreceptor (page 193), responding to changes in the chemical composition of the blood passing through its capillaries. Although its structure is suggestive of endocrine organs, no internal secretion is known.

The carotid body should not be confused with the **carotid sinus**, which is a dilatation in the wall of the internal carotid artery at its origin. The carotid sinus has a rich network of pressor-receptor nerve endings (page 193) in the outer part of its wall adjacent to the thinned tunica media These respond to changes in blood pressure.

Two other structures like the carotid body, which also arise in relation to aorta arches of the embryo, are the aortic and supracardial bodies.

LYMPHATIC VESSELS

A system of closed **lymphatic vessels**, starting as blind capillaries in the various tissues of the body, serves to pick up fluid and take it back

[6] See Visual Aids, 20.

superior vena cava as well as in much of the inferior vena cava (Fig. 103).

The adventitia is the thickest coat of the veins. It is formed largely by fibrous connective tissue but contains longitudinal smooth-muscle fibers in many locations. Elastic fibers occur, too, although no external elastic membrane is present. The venae cavae and other large veins have much
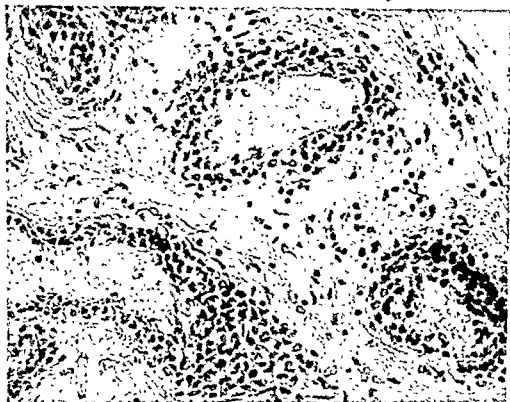
FIGURE 104. Arteriovenous anastomoses (4 channels) in the human coccygeal body. Smooth-muscle nuclei of very short muscle fibers are numerous, giving the vessel walls an endocrine appearance. Specimen in the Piersol collection. Photomicrograph, 300 ×.

rather evenly distributed longitudinal smooth muscle in the adventitia (Fig. 103). Prominent longitudinal bundles of muscle are also found in the outer coat of the portal and renal veins and give an especially lopsided appearance to the suprarenal veins.

ARTERIOVENOUS ANASTOMOSES

Capillaries connect arteries and veins in most tissues of the body, but they are not the only ways by which blood circulates. Sinusoids, forming another type of connecting link, have been mentioned. In many locations, arterioles anastomose directly with venules and provide short-circuiting

the course of the collecting lymphatic vessels. The fluid conveyed by most of the capillaries and smaller collecting vessels is clear and resembles blood plasma. After passing lymph nodes it contains lymphocytes. Lymphatic vessels in the villi of the small intestine and in the mesenteries are called **lacteals.** They hold white lymph, called **chyle,** during digestion of a fatty meal. A good way to see lymphatic capillaries and collecting vessels is to feed an animal cream and subsequently open its abdomen under an anesthetic to observe lacteals.

Lymphatic capillaries are composed of endothelial cells held together by a minimum amount of interstitial substance. They closely resemble blood capillaries, although they are a little wider and usually appear collapsed in histological preparations. Lymphatic capillaries branch and anastomose to form plexuses in the loose fibrous connective tissue. In the skin, these tend to be more deeply placed than the blood capillaries.

Collecting lymphatic vessels receive lymph from the capillaries and conduct it through lymph nodes into the large lymphatic ducts. Small collecting lymphatics resemble venules. A comparison is shown in Figs. 93D and E; also in Fig. 105. See how thin they are. Three coats can be recognized in those greater than 0.2 mm. in diameter. The layers are incomplete in the medium-sized lymphatic vessels. The tunica intima is formed by endothelium and a little delicate fibrous connective tissue. The tunica media has circular smooth-muscle fibers arranged in spirals.

Proportionally more circular muscle occurs in the larger lymphatic vessels than is found in veins of comparable size. The tunica adventitia is principally fibrous connective tissue with a few longitudinal muscle fibers. There are few elastic fibers. Numerous valves are formed by folds of the tunica intima of all the collecting lymphatic vessels.

The boundaries between the three coats of the large lymphatic ducts are rather indistinct. The **thoracic duct,** illustrated in Fig. 105B, is the greatest of the lymphatic vessels and closely resembles a vein. It and other large lymphatic vessels are supplied with blood vessels and motor nerve endings for their scanty smooth muscle.

Since lymph arises in blind capillaries, it is not propelled by the force of the heart beat. It is moved by the contraction of skeletal muscles in the vicinity and by tissue fluid pressure generated by filtration of fluid from the blood capillaries. Lymph flow is relatively sluggish, and lymphatic pressures are slight. Some active contraction of larger lymphatic vessels is rhythmical and may aid in moving the fluid.[7]

[7] See Visual Aids, 22.

to the subclavian veins at the root of the neck. A few organs, notably the central nervous system and the bone marrow, lack lymphatic vessels.
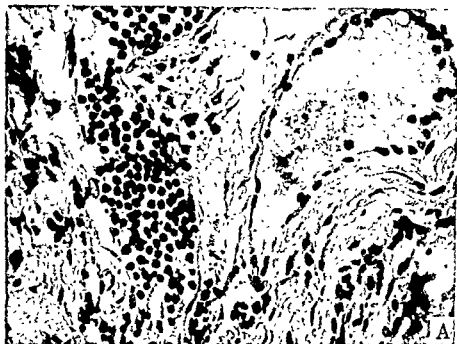
FIGURE 105 Lymphatic vessels: A, lymphatic capillary full of lymphocytes (left), and venule containing a little blood (right) in the stroma of a human tonsil, B, thoracic duct of a monkey. Photomicrographs, A, 300 ×; B, 130 ×.

Lymphatics in skeletal muscle appear to be confined to the connective-tissue septa. They are absent in liver lobules and around lung alveoli.

Lymph nodes, the places where lymphocytes are formed, occur along

Lymphatic Tissue and Organs

Loose connective tissue harbors slightly differentiated cells comparable with those of embryonic mesenchyme. In places where these are numerous, they constitute reticular tissue. The cells of reticular tissue can become any one of a number of types, notably fibroblasts, macrophages, and hemocytoblasts. The loose connective tissue beneath the epithelium of the digestive tract, and to a lesser extent that in the respiratory tract, is full of reticular cells, reticular fibers, and lymphocytes. Many lymphocytes may come from other places by way of the blood stream, but some are formed there. Foci of generation of lymphocytes are present beneath the epithelium, from the tonsils through the large intestine.

LYMPHATIC TISSUE AND NODULES

Reticular cells, with their outstretched processes, construct a meshwork in the subepithelial layers of the digestive tract. This is filled with tissue fluid swarming with lymphocytes which either float or become lodged among the branching processes of the reticular cells. The combination of reticular tissue and lymphocytes is called **diffuse lymphatic tissue.** Many of the reticular cells forming its stroma possess delicate reticular fibers.

Some reticular cells differentiate into macrophages. Others become blood-forming cells, the hemocytoblasts, which ordinarily give rise only to the lymphocytic line in this location. Where the immediate derivatives of hemocytoblasts, lymphoblasts, accumulate in diffuse lymphatic tissue, little centers for genesis of more lymphocytes are formed. These are called **lymphatic nodules** (Fig. 106). Frequently you will encounter **solitary nodules,** but occasionally they are found in groups or **aggregate nodules,** as in the tonsils (Fig. 192), intestine, and vermiform appendix.

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A feature of the diffuse lymphatic tissue beneath epithelium is migration of its lymphocytes into the epithelium and on through it into the lumen of the organ. This migration may be so extensive that the epithelium appears eroded, as it does in the crypts of the tonsils (Fig. 193). In other regions, it may involve only a few lymphocytes. It fluctuates widely with varying conditions in the digestive tract, but it is never insig-
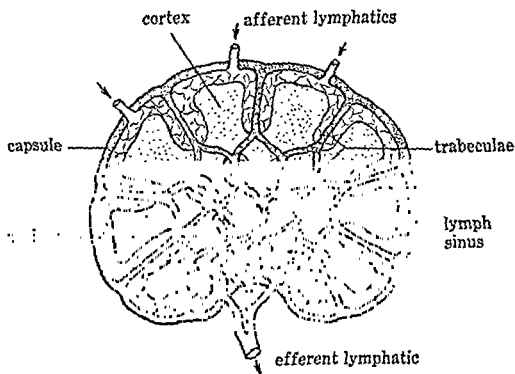
FIGURE 107. Diagram to illustrate structural plan of a lymph node.

nificant. More dramatic than the suicidal migration of the lemmings, hundreds of millions of lymphocytes crawl through the interstitial substance of the intestinal epithelium each day and plunge into the digestive flood.

LYMPH NODES

Lymph nodes are encapsulated masses of lymphatic tissue measuring from 1 to 30 mm. in diameter, often found in groups along the course of lymphatic vessels. They are easily seen in dissection of the mesenteries and in the axilla and groin; they occur in many other places as well. They are little organs made up of a fibrous connective-tissue and reticular-tissue stroma and a parenchyma of lymphocytes. Arterioles and venules enter the lymph node at an indentation, called the **hilus,** and course

Formation of lymphocytes is not confined to the lymphatic nodules but can occur in diffuse lymphatic tissue. Lymphopoiesis was described in Chap. 4.

Lymphatic nodules are absent at birth and are inconstant in the adult. You may be certain of finding them present in many locations, but those in existence today may not remain throughout life. They wax and wane, appearing in one place now and disappearing later.
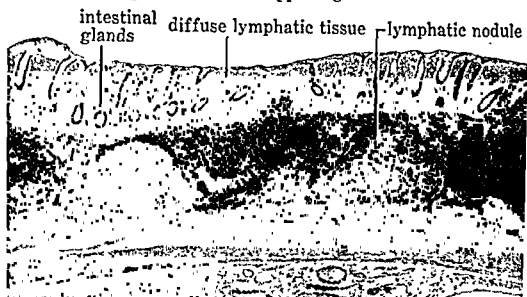
FIGURE 106. Diffuse lymphatic tissue and lymphatic nodules in a longitudinal section of the human appendix. Specimen from Prof. R. F. Becker. Photomicrograph, 40 ×.

A lymphatic nodule starts to form, some say, in response to an inflammatory reaction in which there is an active proliferation of a small focus of lymphoblasts or large lymphocytes in diffuse lymphatic tissue. Since lymphoblasts have more cytoplasm and less chromatin in their nuclei than small lymphocytes, the proliferating group, or **germinal center,** will appear more lightly stained than the surrounding diffuse lymphatic tissue. As the proliferative process goes on, a marked ring of small dark lymphocytes may appear around the germinal center because of growth pressure (Fig 106).

Regression of lymphatic nodules occurs when proliferation of the lymphoblasts ceases. The last divisions produce small lymphocytes which then come to occupy the germinal center. The whole region stains darkly again. A peripheral ring of lymphocytes vanishes when growth pressure is removed. Intense activity may temporarily leave a pale reaction center filled with reticular cells and macrophages.

ules with germinal centers (Fig. 108). Diffuse lymphatic tissue passes
in from the cortex toward the hilus to form medullary cords. Surround-
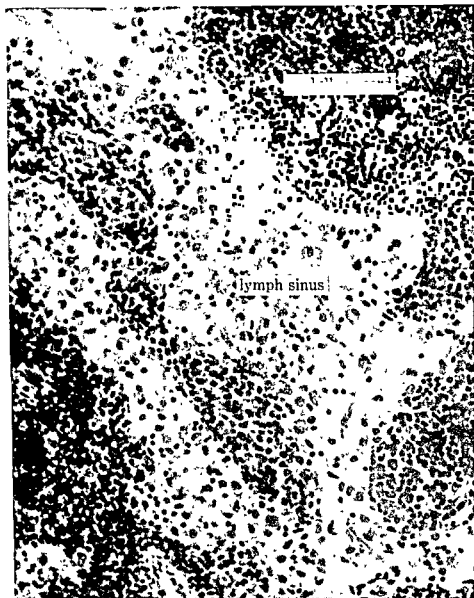
FIGURE 109. Medullary cords and a lymphatic sinus of a human lymph
node Photomicrograph, 300 ×.

ing the larger cortical masses and separating these and the smaller medul-
lary cords from the capsule and trabeculae are the **lymphatic sinuses.**

Sinuses are fluid-filled spaces traversing the lymph nodes. You often
find few lymphocytes; and the reticular stroma is usually well portrayed
in histological sections of the sinuses. The sinuses are extensively baffled

throughout the interior in fibrous connective-tissue trabeculae, which are septal projections of the capsule.

The **capsule** and **trabeculae** of the lymph node are dense fibrous connective tissue containing a few smooth-muscle cells occasionally. Small nodes have slight trabeculae. Large nodes have heavier bands and septa
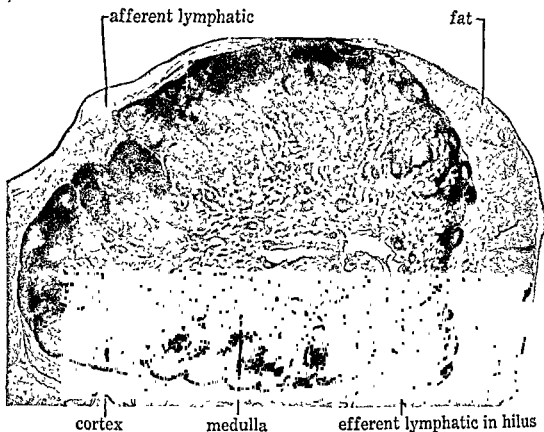
FIGURE 108. Lymph node in the human mesentery sectioned through the hilus. Photomicrograph, 10 ×.

of connective tissue to break the lymphatic tissue into compartments. Trabeculae carry the blood vessels and a few nerve fibers. They form the major skeleton of the lymph nodes, as shown diagrammatically in Fig. 107.

The finer framework, or stroma, is formed by reticular cells and fibers just as in other lymphatic tissue. Reticular fibers become continuous with collagenous fibers at the capsule and trabeculae, where the reticular stroma is particularly well defined.

Lymphatic tissue of lymph nodes is usually divisible into an outer more compact **cortex** and an inner looser **medulla**. The medulla reaches the surface only at the hilus. The cortex contains a variable number of nod-

is an organ of unknown function and goes through some interesting age changes. Relatively largest in the fetus, it reaches maximum actual size during adolescence. Exclusive of its fat, it weighs about 12 gm. at birth, doubles in weight by the fourteenth year, returns to birth weight by the twentieth, and then declines to 1.5 gm. or less by age fifty-five.

cortex   medulla
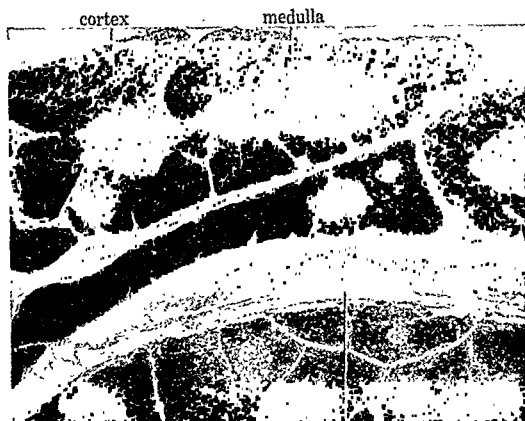
FIGURE 110. Thymus of a child. Photomicrograph, 25 ×.

The thymus consists of many lobules of lymphatic tissue separated by fibrous connective tissue containing blood vessels and lymphatics. The stroma is formed by reticular cells and fibers. The parenchyma is made up of lymphocytes.[1] In other words, the organ is made of the same kind of tissue as the lymph nodes. However, it differs markedly from lymph nodes in a number of particulars. It lacks lymphatic sinuses, and there are no afferent lymphatic vessels going to the thymus.

The cortex is sharply delimited from the medulla (Fig. 110). It is

[1] Because the thymus develops from the third branchial pouches of the embryo and is thus entodermal, some writers are loath to consider its stroma as a true reticular tissue. Similarly, they do not wish to regard the parenchymal cells as lymphocytes but noncommittally call them **thymocytes.**

channels through which lymph circulates slowly. In addition to the primitive nonphagocytic reticular cells lining them, many macrophages are found there. Some of the macrophages are attached to the walls of the sinuses, and others are free. Sinuses are illustrated in Fig. 109.

Lymph enters the peripheral cortical sinuses from **afferent lymphatic vessels** which perforate the capsule. Endothelium of these vessels merges with the reticular lining network of the lymphatic sinuses. Valves occur in the afferent vessels near their entrance into the nodules. Lymph filters through the system of cortical and medullary lymphatic sinuses, where the macrophages have opportunities to phagocytize foreign material, bacteria, etc.

Lymph leaves the lymph nodes at the hilus by way of **efferent lymphatic vessels.** These, too, possess valves, permitting lymph to flow only away from the node. If the lymph entering the node has not previously passed through lymphatic tissue, it is almost noncellular; but it leaves with many lymphocytes which it has gathered in the sinuses. Afferent and efferent lymphatics are shown in Figs. 107 and 108.

Lymph nodes produce lymphocytes. They also serve as stations for phagocytosis by macrophages. However, do not depend too much upon this latter function, for the macrophages of lymph nodes do not stop all bacteria, viruses, foreign particles, and cancer cells that come their way. By-passes may exist. It is more important to think of lymphatic vessels and their nodes as a system along which infection can quickly spread than to rely upon the lymph-node macrophages to stop infections.

TONSILS

The structure of **tonsils** will be considered in Chap. 17. They are masses of lymphatic tissue containing aggregate nodules beneath the epithelium of the pharynx. The palatine tonsils are encapsulated organs. The pharyngeal and lingual tonsils are nonencapsulated. All possess crypts of epithelium which extend into their substance and which exhibit lymphocytic infiltration to a marked degree. No afferent lymphatic vessels enter the tonsils, but efferent vessels convey lymphocytes away from them (Fig. 105A).

THYMUS

The **thymus** is a mass of lymphatic tissue in the upper thorax, located in front of the pericardium and great vessels at the base of the heart. It

in old age, thymic corpuscles exist, and a little lymphatic tissue is found around them. The form of the organ is maintained by the replacing fat. Figure 112 illustrates involution of the thymus.
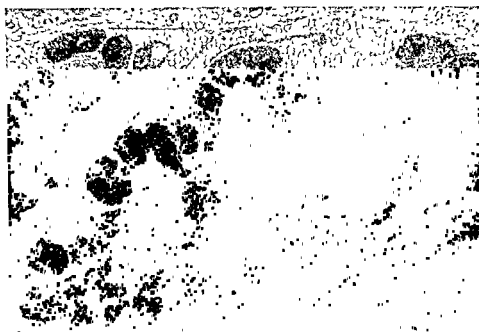
FIGURE 112 Thymus of 39-year-old man, showing involution and replacement by fat. Compare with Fig 110. Photomicrograph, 25 ×.

SPLEEN

The spleen produces lymphocytes and destroys red blood corpuscles. It contains the largest amount of lymphatic tissue in the body. It is very different from other lymphatic organs because its sinuses are filled with blood instead of lymph. In the embryo the spleen produces red blood corpuscles for a while but does not normally do so after birth. Although its functions are of considerable importance, they are shared with other organs, and so the spleen is not indispensable. Its histological complexity is disproportional to its importance.

The spleen has a very heavy **capsule.** This and its **trabeculae** are composed of dense fibrous connective tissue containing unusually great numbers of elastic fibers and a good many scattered groups of smooth-muscle fibers. The muscle fibers are partly responsible for the rhythmical changes in splenic volume. A hilus admits the splenic arteries, veins, and nerves, all of which course for some distance in the system of branching trabeculae.

formed by dense masses of lymphocytes enmeshed in rather scanty stroma. The medulla contains many reticular cells but fewer lymphocytes than the cortex. Macrophages are present. Lymphatic nodules and germinal centers are usually absent.

cortex
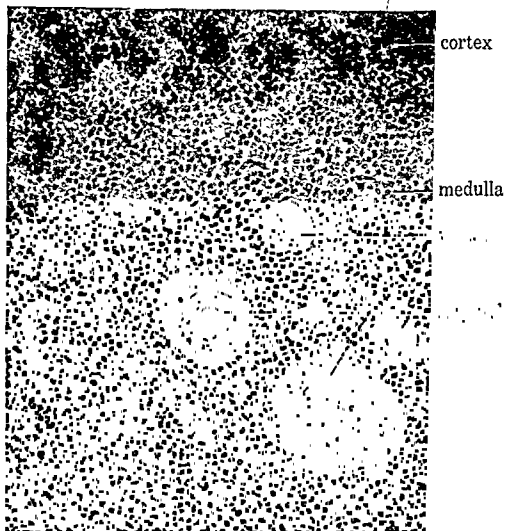
medulla

FIGURE 111. Thymic corpuscles in the thymic medulla of 14-year-old girl. Photomicrograph, 300 ×.

Rounded masses of concentrically arranged degenerate cells form bodies known as **thymic corpuscles** (Hassall). These are confined to the medulla. They measure 30 to 100 μ in diameter and stain well with acid dyes, such as eosin. They are illustrated in Fig. 111.

The usual description of thymic structure applies to the organ during infancy. Involution begins before adolescence with gradual thinning of the cortex and replacement of adipose tissue. This is a slow process. Even

in the splenic nodules, are called **central arterioles** (Fig. 114). They are not accompanied by veins. Occasionally two central arterioles are seen in one nodule near a point of branching.
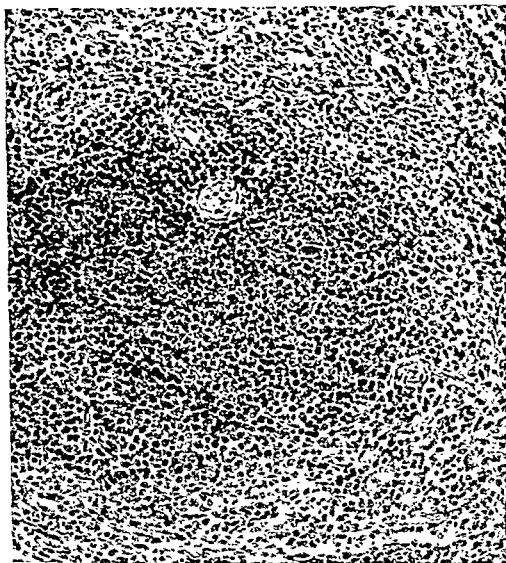
FIGURE 114 Splenic corpuscle, showing an eccentrically placed central arteriole, above which is a smaller branch. Photomicrograph, 300 ×.

Branching continues for some distance, and smaller arterioles ultimately pass among cords of red pulp, having lost their adventitia with its white-pulp lymphocytes The diameter of the artery diminishes from about 200 μ as it leaves the trabeculae to 40 μ as it leaves the white pulp. During the first and longest part of their course through the red pulp, branching sprays of arterioles possess single layers of smooth muscle but no

The trabeculae break the spleen up into a series of compartments or lobules which are filled with the *splenic red pulp*. Red pulp is modified lymphatic tissue of the diffuse type, arranged in poorly defined cords accompanied by the peculiar splenic venous sinuses. Traversing the lobules of red pulp are the arteries of the spleen, some of which have more com-
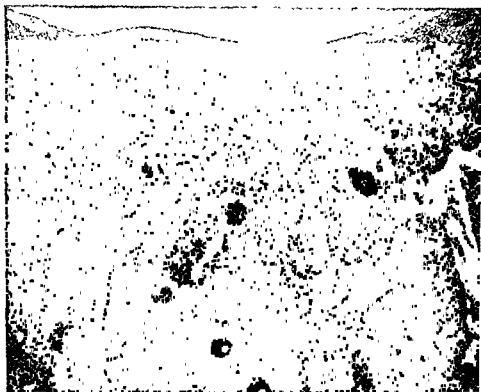
FIGURE 113. Spleen of man. Note the heavy capsule and trabeculae (light bands), the splenic corpuscles (dark spots), and red pulp (main gray bulk). Photomicrograph, 25 ×.

pact masses of lymphocytes about them, forming the **white pulp**. In cross sections, the white pulp appears as circular masses. called **splenic nodules,** which are the dark spots in Fig. 113. Some of these possess germinal centers.

Branches of the splenic artery enter the hilus and undergo further branching, which distributes them throughout the trabecular system. These **trabecular arteries** are of the small muscular type. Their adventitial coat blends with the dense fibrous connective tissue of the trabeculae. They are accompanied by **trabecular veins** draining the spleen.

When the arteries leave the trabeculae, the fibrous adventitia is replaced by reticular connective tissue, which becomes packed with lymphocytes to form the white pulp. These little vessels, eccentrically placed
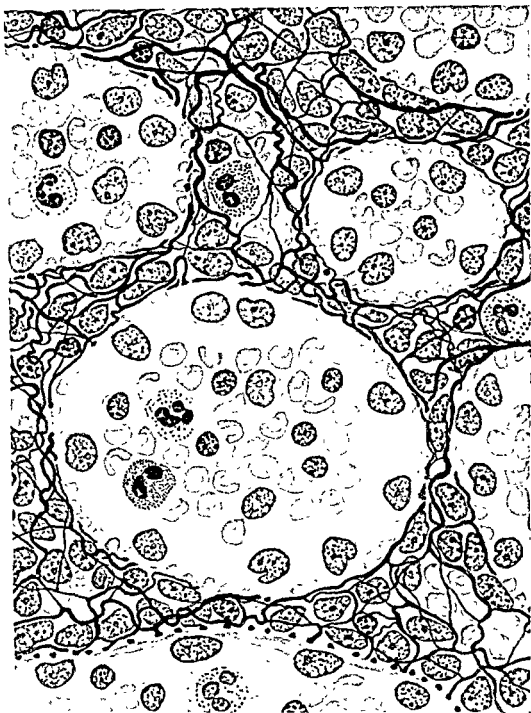
FIGURE 116 Splenic sinuses and red pulp (human), showing reticular fibers The sinuses contain blood corpuscles The sinus at the bottom is sectioned longitudinally and shows its encircling reticular fibers cut across. Silver carbonate stain. 900 ×.

adventitia. These are the **pulp arterioles.** When the muscle disappears with further branching, a peculiar thickened wall appears as a consequence of addition of concentrically arranged reticular cells adjacent to the endothelium. These vessels are called **sheathed arterioles;** they are less prominent in man than in some other species. **Arterial capillaries** are
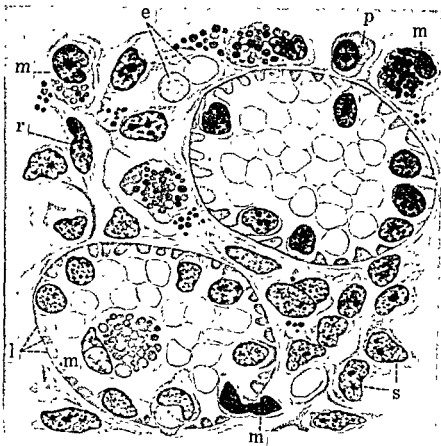
FIGURE 115 Splenic sinuses and red pulp: *e,* red corpuscles in pulp, *l,* thin cytoplasmic portions of cells lining a splenic sinus; *m* and *s,* macrophages in the pulp and in a sinus; *p,* plasma cell; *r,* reticular cell. 900 ×.

the finest ramifications of the arterial tree. They connect with the venous sinuses and with collecting venules coursing in the red pulp.

Splenic sinuses are wide channels with thin walls formed by elongated cells that bulge into the lumen. These cells resemble the staves of a barrel. Circularly arranged reticular fibers form the hoops. The lining cells (littoral cells) are not endothelial but are macrophages. The sinuses occupy much room in the red pulp, crowding the cords of loose lymphatic tissue, as seen in Figs. 115 and 116. They connect with small venules in the red pulp, which, in turn, drain into larger venules in the trebeculae.

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   through a quartz rod has been developed by this investigator. His experi-
   ments on the spleen offer an outstanding example of what can be accom-
   plished in overcoming difficulties.*

The walls of splenic sinuses appear to be intact in the living animal. Most blood corpuscles are confined within them. However, these walls are extraordinarily fragile, and removal of the spleen for its histological preparation induces extravasation of blood into the red pulp. This makes it difficult to differentiate between sinuses and pulp cords in histological sections.

Results of investigation of the circulation through the splenic pulp are contradictory. Some lead to the view that the sinus walls normally are lattice-like and permit red corpuscles to pass freely out among the macrophages and lymphocytes of the splenic cords. However, closed venous sinuses have been observed in living animals, and it would seem that the successful positive observation of them should outweigh other negative evidence. Under normal healthy conditions, the sinuses are filled with blood that becomes stagnant, permitting some of the plasma to seep through their very thin walls. A few red corpuscles, perhaps only those whose useful lives are over, accompany the plasma out into the pulp.

Intermittent closure of the venules permits engorgement of the splenic sinuses and subsequent concentration of the formed elements of the blood, at which time some of the plasma filters out of the walls. The volume of the spleen increases when many sinuses become filled with blood. Large volumes of red corpuscles can be stored in this way. Contraction of the smooth muscle of the splenic capsule and trabeculae, as well as contraction of the arterioles, accompanied by the opening of the venous channels through the spleen, provides means of quickly adding corpuscles to the circulation.

Red corpuscles that have become spent after their one hundred or more days in circulation are apt to be destroyed in the spleen. Macrophages lining the sinuses can phagocytize them or can pass them on to the macrophages in the splenic cords of lymphatic tissue. Stages in red corpuscle destruction are easily seen in routine sections of the spleen. Macrophages of many different appearances can be observed. Stages intermediate between lymphocytes and monocytes and between monocytes and full-grown macrophages will be encountered.

The spleen is one of the greatest sources of lymphocytes, but there are no lymphatic vessels to carry them away. Although a very few small lymphatics occur in the capsule, they do not drain the pulp. Lymphocytes make their way from the splenic nodules, where most of them arise, into the splenic cords. Thence, they crawl through the thin walls of the splenic sinuses into the sluggish or static blood stream.

processes are less than 1 mm. long, or only about two hundred times as long as the diameter of their cell bodies.

Neurons are the structural units of nervous tissue, but these units always function in cooperating groups and chains, one receiving and passing the excitation on to another until finally somewhere in the body an effect is manifested. Reflex arcs are the physiological units. One of the processes of a neuron ordinarily conducts toward another neuron in a reflex arc or toward an effector organ like a muscle, outside of the nervous system. That process is the **axon.** Most neurons have numerous other processes, shorter than axons, which ordinarily conduct toward the cell center. They are the **dendrons.** The junction of one neuron with the next, a simple contact between two plasma membranes, is designated the **synapse.**

Neurons exhibit greater variety of shapes and sizes than any other kind of cell. The smallest are only about 5 μ, the largest, 200 μ in diameter of the cell body. The smallest usually have thin and short axons, the largest, heavy and long axons. Various shapes will be seen in illustrations accompanying this chapter, especially in Figs. 117 to 119.

Neurons are long-lived and hardy. Specialized to the extreme, they have lost the power to divide. Although centrosomes have been observed, there is no evidence that cell division occurs after the first year postnatally. As though to compensate for inability to provide replacements, an enormous excess of neurons exists in some parts of the nervous system. You utilize only a fraction of those you have and never miss the loss of one here and there. Neurons do die in the process of aging. They are not replaced. It is remarkable that so many live for so long. They are more resistant to the ravages of time and a succession of insults by noxious agents than many others of the body's cells. Yet they are remarkably sensitive to traumatic injury to their processes and do their best to repair such injuries. They cannot tolerate, even briefly, an environment lacking oxygen.

Neurons are not the only cells of nervous tissue. Closely associated with them in the central nervous system are others known as **neuroglia.** They are not found outside the central nervous system, but another type of nonnervous cell does occur in the ganglia and nerves of the peripheral nervous system. It is the **neurolemma** cell, which takes part in forming capsules of nerve cells in the ganglia and sheaths on the nerve fibers. Neurons, neuroglia, and neurolemma have a common embryonic origin from the ectoderm of the neural tube and neural crest.

Nervous Tissue and the Peripheral Nervous System

N ervous tissue is the last one of the fundamental tissues to be considered. It is formed by neurons and associated cells, the neuroglia, and the neurolemma. The nervous system is the sum total of all nervous tissue. Although it comprises only about 3 per cent of the weight of your body and is mainly water, it is most important. The greatest accumulation of nervous tissue forms the central nervous system, *i.e.*, the brain and spinal cord, and is contained within tough fibrous membranes. Elsewhere, in the peripheral nervous system, it exists in association with connective tissue, muscle tissue, and epithelial tissue. It is everywhere supplied with blood vessels. The interstitial substance of nervous tissue is tissue fluid which, in and around the brain and spinal cord, accumulates in a measurable quantity of cerebrospinal fluid.

ELEMENTS OF NERVOUS TISSUE

Neurons, the most specialized cells of nervous tissue, possess to a high degree two of the fundamental properties of protoplasm: capacity to react to stimuli, and ability to conduct an excitation rapidly to distant portions of their cytoplasm.

Neurons have adapted themselves to the need for distance conduction by extending extraordinarily thin protoplasmic processes, their axons and dendrons. The longest neuron process, although only a few microns thick, may course for a distance of a meter. Such a process is some sixty thousand times as long as the diameter of the cell at its nucleus. Other

Because the processes of neurons commonly extend for considerable distances away from the cell body, it is rarely possible to observe a neuron in its entirety in histological sections. The bodies of neurons tend to be grouped in clusters within the brain, as well as in ganglia outside the central nervous system. Their processes tend to run parallel to one
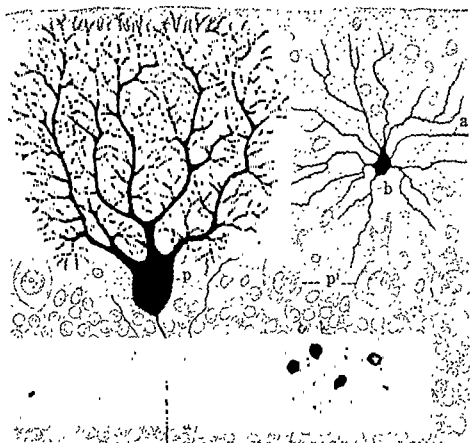
FIGURE 118 Cerebellar neurons of three types illustrating marked variations: *b*, basket cell, *g*, granule cells, *p* and *p'*, Purkinje cells, *a*, axon; *c*, collateral branches of axon. Golgi stain, semidiagrammatic

another in bundles comprising the fiber tracts of the brain and the nerves of the peripheral nervous system. Consequently, it is convenient to study nerve-cell bodies and nerve-cell processes separately, speaking of them, respectively, as **nerve cells** and **nerve fibers**. Do not let this artificial separation lead you into any misconception. Nerve fibers are parts of nerve cells.

Nerve cells and nerve fibers can be seen in preparations stained with the usual dyes, such as hematoxylin and eosin, and it is desirable to be able to recognize them when you encounter them in various organs. A
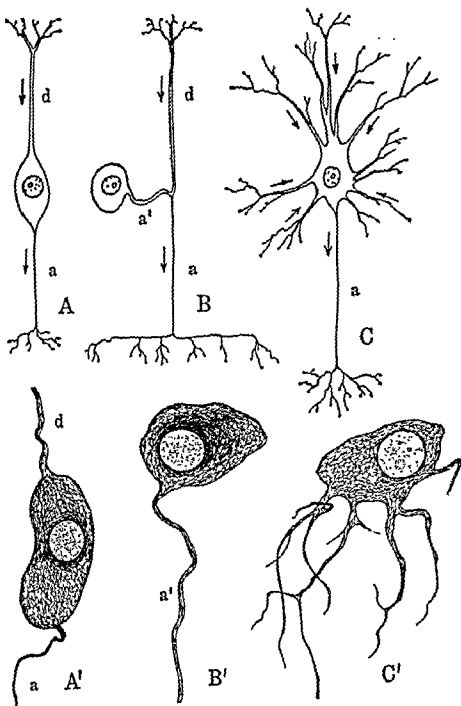
FIGURE 117. Neurons (diagram and cell) of three types found in the peripheral nervous system· A and A', bipolar neurons of the acoustic ganglion, B and B', unipolar neuron of other craniospinal ganglia; C and C', multipolar neurons of autonomic ganglion; a, axon a", process common to axon and dendron, d, dendron. Arrows in the diagrams indicate direction of conduction.

Nucleus: The nerve cell nucleus has a rather characteristic appearance, which varies only a little with size and shape of neurons. The usual type of nucleus is vesicular and poor in chromatin. It has a well-developed nuclear membrane. The feature of greatest prominence in the nucleus is the nucleolus, although usually single, two are not uncommonly seen. The nucleolus is a spheroidal body of homogeneous appearance which stains brilliantly and metachromatically[2] with some basic dyes used in Nissl methods. The ratio between nuclear size and size of cell body is fairly constant; large nuclei in large cells, small nuclei in small cells.

Neurofibrils: Regardless of shape or size, all neurons possess neurofibrils in the cytoplasm. These exist in some form in living cells. They are best observed in the large nerve cells of the central nervous system stained by silver methods (Figs. 119 and 120). They appear as multiple delicate threads coursing across the cytoplasm from one process into another. They are quite prominent in nerve cells of young animals and fetuses. Neurofibrils are contained within each individual neuron and do not pass across synapses into others. Their function is unknown.

Chromophil substance: Flakes or granules of basophilic chromophil substance are present in the cytoplasm of nearly all nerve cells except, perhaps, the very smallest. Various Nissl methods are used to display these particles, which are commonly designated **Nissl bodies** (Figs. 119 and 120). The patterns that they form in the cytoplasm are definite and constant within groups of neurons of similar structure and function, but vary from one type of nerve cell to another. The patterns can be varied with different chemical solutions used to fix the tissues. Although Nissl bodies have not been seen in living cells, there is indirect evidence that they represent some preformed substance there. It is not known what function they serve.

Traumatic damage of nerve cells or nerve fibers causes dispersion or alteration in the pattern of the chromophil substance. Asphyxiation of nerve cells brings about its destruction and disappearance in a few hours The neurons are said to undergo **chromotolysis** when their Nissl bodies disappear as a result of neuron damage. Somewhat similar changes appear in nerve cells a few hours after death. These are frequently mistaken for significant pathological manifestations.

Nissl bodies are not found in all the processes of neurons They extend some distance out into dendrons of large multipolar nerve cells (Fig. 120) but are not usually encountered in the axon. In fact, the

[2] Staining in a tint different from that usually obtained.

great deal more can be learned about nerve cells and nerve fibers by using special staining methods, developed specifically for studying the nervous system. Neurological staining methods fall into four main categories. First, there are the techniques that stain the basophilic chromophil bodies of the neuron cytoplasm. These are called the **Nissl stains**. Second, there are the methods that bring out cytoplasmic neurofibrils, rendering visible the fine nerve fibers and terminations. We shall refer to these as the **silver stains**. In the third category there are the several **sheath stains** that color myelin sheaths of nerve fibers. Finally, a number of techniques have been developed for differentiating neuroglia. These are the **glia stains**. This is the barest possible outline of a subject on which volumes have been written.

Your concept of nervous tissues gained by studying fixed and stained preparations is apt to be imperfect at best unless you can supplement it with observations on living neurons. Although it is doubtful if you yourself can prepare tissue cultures of nerve cells or even observe demonstrations of them, you may be able to see motion pictures of living, growing nerve fibers.[1]

CYTOLOGY OF NERVE CELLS

Nerve cells vary so widely in size and shape that selection of any one as a typical example for description of its intrinsic structure is arbitrary. The smallest are smaller than a lymphocyte; the largest are visible to the naked eye. Some have many processes; others, only one. Globoidal, piriform, spindle-shaped, pyramidal, and stellate nerve cells are encountered. Cells with many processes, *i.e.*, multipolar neurons and particularly the stellate variety, outnumber other types. Among them, the neurons $40\,\mu$ or more in diameter most clearly portray details of cell structure. Note especially Figs. 119A, B, E, and 120.

Nerve cells lack a true cell wall but present a cytoplasmic surface to the surrounding tissue fluid. As in other types of cells, diffusion of metabolic substances takes place through this surface membrane. Transmission of nerve impulses occurs across it.

The cytoplasm, called **neuroplasm**, is viscous and looks homogeneous in the fresh condition. In it are the nucleus, organoids, and inclusions, which are found in all cells, and two particularly characteristic structures, the **neurofibrils** and **chromophil substance**.

[1] See Visual Aids, 23 and 27.

FIGURE 120 Multipolar motor neurons of the spinal cord: *A*, guinea pig, *B*, newborn kitten Chromophil substance stained by Nissl method in *A*; neurofibrils stained by silver method in *B* Photomicrographs, 900 ×.

help build no fiber tracts, but they ramify in the vicinity of the nerve cell. Long dendrons of unipolar and bipolar neurons of sensory ganglia have a structure exactly like the axons of these cells.

cytoplasm near the origin of the axon often lacks them. This clear cone-shaped region is called the **axon hillock** (Fig. 119A), an inconstant
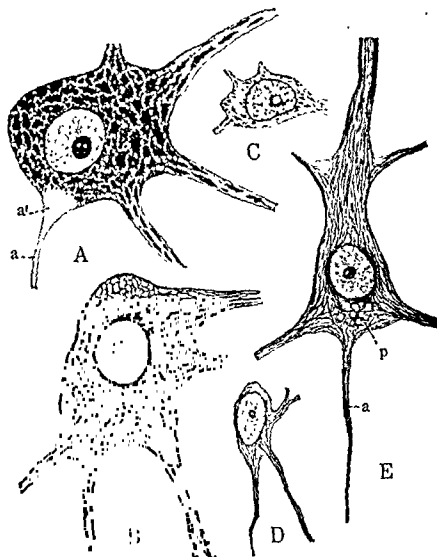
FIGURE 119. Multipolar neurons. *A* and *B*, motor cells of a kitten's spinal cord stained by Nissl and silver methods; *C* and *D*, small interneurons of the spinal cord stained by Nissl and silver methods; *E*, neuron of the cerebral cortex stained by silver; *a*, axon; *a'*, axon hillock, *p*, pigment 900 ×.

structure even in the largest cells. Many small and medium-sized multipolar neurons have no axon hillocks.

Processes: The neuron processes that ordinarily conduct impulses toward the cell body are **dendrons.** Dendrons of sympathetic ganglion cells and of those within the brain and spinal cord are short processes. Many of them are extensively branched. They acquire no sheaths and

neuron in a reflex chain. This takes a little time, although very little; it delays transmission no longer than 0.006 sec.

NERVE FIBERS

The term nerve fiber is usually reserved for the long axon or the long peripheral dendron plus the sheaths they may acquire. The nerve fiber has a core, the **axis cylinder** of the fiber. This is a drawn-out portion of the neuron cytoplasm and is made of viscous protoplasm. The cytoplasm of the axis cylinder is known as **axioplasm**. It is not a static material, for it flows out from the cell body. It contains neurofibrils but no chromophil material.

Many nerve fibers are sheathed axis cylinders. Throughout the entire nervous system, **myelin sheaths** are prevalent. They are made of a mixture of lipoids, which gives the living or freshly killed **myelinated nerve fiber** its white, glistening appearance. The white matter of the brain and spinal cord contains great numbers of nerve fibers with myelin sheaths.

There are many more nerve fibers that have no myelin sheaths. They are the **unmyelinated nerve fibers.** As a general rule, they are the very thin fibers. Thick ones acquire myelin sheaths.

Certain structural details of the myelin sheaths can be observed in peripheral nerve fibers when appropriate methods are used to stain and observe them. Since myelin is lipoidal, it is dissolved by the fat solvents used in most procedures. The solvents used in the silver method leave only spaces where the myelin was located (Fig. 122A). The sheath stains, especially solutions of osmic acid, stain myelin dark, as shown in Fig. 122B When viewed in longitudinal planes, it shows unstained diagonal clefts, the **incisures** (Lantermann) seen in Fig. 123A These have been demonstrated in the sheath of the living fiber. After hematoxylin and other types of staining, a delicate network of some refractive substance may appear in place of the myelin (Fig. 123B) This is called **neurokeratin** and is probably nothing but the precipitated protein component of myelin.

Outside of the central nervous system in the peripheral nerves and ganglia, all nerve fibers have an additional sheath, which is cellular It is formed by **neurolemma** cells. The cytoplasm of these cells is stretched like sausage casing over the myelin sheath (Fig 123C). Neurolemma cell nuclei can be seen along nerve fibers stained by the ordinary methods (Fig. 123B), but you will find it difficult to see the neurolemma cyto-

The processes of nerve cells that conduct away from the cell are **axons.** The vast majority of neurons of the brain and spinal cord give rise to axons that end within the brain and spinal cord. Other axons come into the central nervous system from the sensory ganglia. Only the motor neurons[3] send their axons out of the central nervous system,
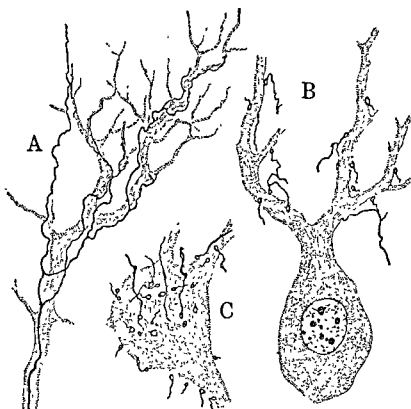
FIGURE 121. Synapses: *A* and *B*, climbing fibers and end bulbs on dendrons of Purkinje cells of the cerebellum, *C*, end bulbs on a motor neuron of the spinal cord. Silver stains.

building the nerves. We shall consider these nerve fibers and their endings presently.

Axons that terminate in the central nervous system branch repeatedly as they approach the groups of neurons with which they make contact. Their final endings appear as thin filaments clasping the bodies of neurons, running parallel to the branches of the dendrons or forming tiny loops, knobs, or **end bulbs,** which come to rest against the surface membrane of the cell body or dendrons (Fig. 121). These are mechanisms of the **synapse,** where nerve impulses arriving along the axon can create an excitation on the surface membrane of dendrons or cell body of the next

[3] And a very few sensory neurons of the trigeminal nerve.

plasm. The neurolemma sheath does not occur in the brain and spinal cord.

On myelinated peripheral nerve fibers, each neurolemma cell covers a
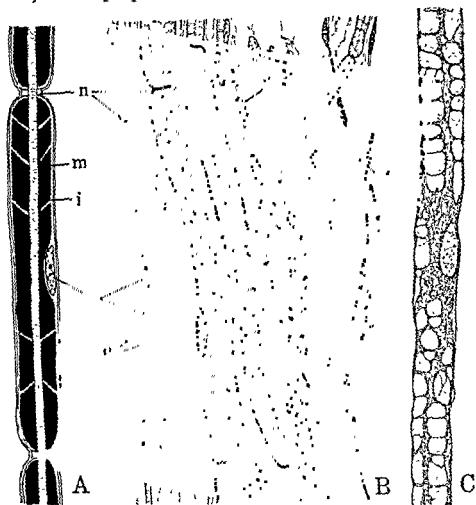
FIGURE 123. Nerve fibers of peripheral nerves, teased preparation stained, A, with osmic acid, B, with hematoxylin after alcohol fixation to show neurokeratin, C, by a special method to show a neurolemma cell c, capillary, e, endoneurium, f, fibroblasts, i, incisure, m, myelin, n, nodes, s, neurolemma nuclei, u, unmyelinated fibers Figure A is a diagram, drawings B and C, 900 ×.

variable linear extent of the fiber Where two cells meet, they constrict the myelin sheath at a **node** (Ranvier), shown in Figs. 123 to 125. Thus, the peripheral myelinated nerve fibers resemble sausage chains whose links are long and thin.

The very thin unmyelinated peripheral nerve fibers often course in tiny bundles through syncytial strands of neurolemma cells. More rarely does
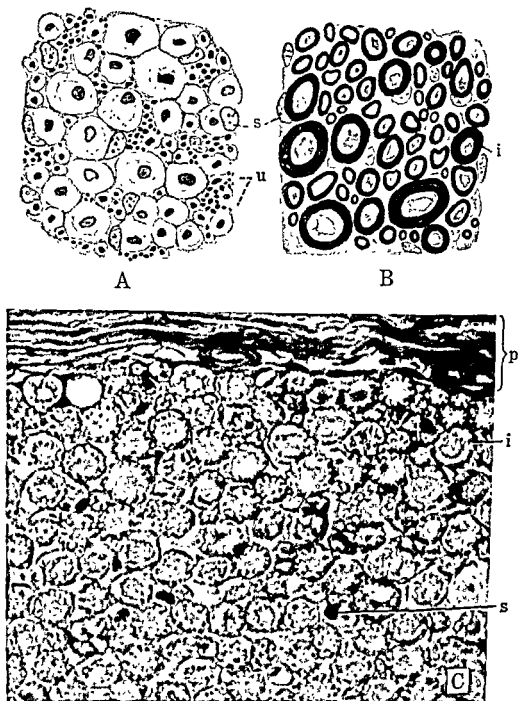
FIGURE 122. Nerve fibers of a peripheral nerve, cross sections stained, A, with silver for axis cylinders, B, with osmic acid for myelin sheaths, and C, with hematoxylin i, myelin; p, perineurium; s, neurolemma nucleus; u, unmyelinated nerve fibers which cannot be seen in B or C. A and B, drawings; C, photomicrograph All, 900 ×

FIGURE 125. Nerve fascicles of the human femoral nerve, stained with hematoxylin Note the dense fibrous connective-tissue sheaths of perineurium and fat cells around them Photomicrograph, 150 ×

an individual unmyelinated nerve fiber possess a separate sheath of its own.

Nodes (Ranvier) break up peripheral myelinated nerve fibers into **internodal segments.** These are longer in thick fibers than in thin ones.
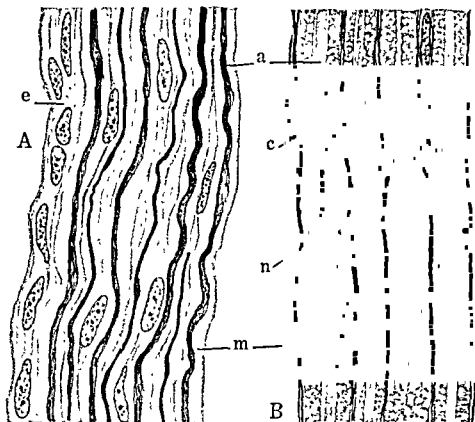
FIGURE 124. Nerve fibers of peripheral nerves in longitudinal sections, A, stained by silver, B, stained by connective-tissue staining technique: *a*, axis cylinders, black in A and gray in B; *c*, fibroblast nucleus; *e*, endoneurium; *m*, myelin, *n*, node in myelin sheath; *s*, neurolemma nucleus. 900 ×.

Branches of myelinated nerve fibers occur only at nodes. Speculation concerning the function of the sheaths of the nerve fiber will be left to others. Certain it is that, by increasing the fiber diameter, the speed of conduction of the nerve impulse is increased.

NERVES

Nerves are bundles of nerve fibers coursing together in fibrous connective tissue supplied with blood vessels and lymphatics. The fibers are of the myelinated as well as the unmyelinated varieties. All possess neurolemma sheaths. Nerves usually have several bundles (called fascicles).

Some small nerves are made up wholly of unmyelinated fibers. Others are entirely myelinated. The human optic nerve has myelinated fibers only. Incidentally, these lack neurolemma sheaths, for the optic nerve is structurally unlike the other cranial nerves, it is actually a fiber tract connecting the retina with the brain (page 226).

FIGURE 127. Spinal ganglion, dorsal and ventral nerve roots and their union to form a spinal nerve. This is a photomicrograph, made many years ago by Prof. G A. Piersol, on a photographic emulsion of his own manufacture.

GANGLIA

Nerve cells grouped in the path of a nerve form a local swelling known as a **ganglion**. Most of the cranial and all the spinal nerves have ganglia near their connections with the central nervous system. Those in the cranium have specific names. Those on the spinal nerve roots are simply called **spinal ganglia**. One is seen in Fig. 127. Besides nerve cells, there are neurolemma cells, fibrous connective tissue, blood vessels, lymphatics, and nerve fibers in a ganglion.

Each of these bundles is bound with dense fibrous connective tissue, the **perineurium**. The perineurium may send septa into the fascicle and partly subdivide it further. The several fascicles of a nerve are embedded in and surrounded by a somewhat looser fibrous connective tissue forming the **epineurium**. Connective-tissue components are shown in Fig. 125
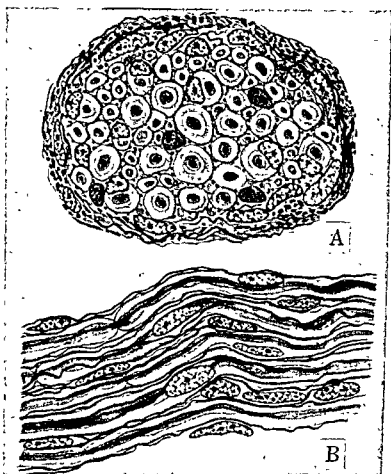
FIGURE 126. Nerve fascicles from a kitten's tongue; silver carbonate stain Note the reticular fibers of the endoneurium among the nerve fibers These appear as fine black dots in *A* and as wavy lines in *B*. 900 ×.

(also 122*C*). Within each fascicle, individual nerve fibers are separated from each other by wisps of delicate connective tissue containing some reticular fibers. This is the **endoneurium** (Figs. 123*B* and 126). Blood vessels and lymphatics that supply nerves pass into the fascicles over perineurial septa and break up into branches with longitudinal orientation.

Nerves vary in fiber composition. The spinal and some cranial nerves have fibers of many sizes. Nerves may serve many different functions. However, each individual fiber has only one specific functional capacity.

The process of each cell pursues a tortuous course for a short distance near the cell, winding about to form what is called a **glomerulus** (Fig. 129). The one process of a unipolar ganglion cell divides into two

FIGURE 129 Spinal ganglion cells The twisted processes are glomeruli. Silver stain 900 ×

branches. The thinner of these branches passes into the nerve root. It is the axon, and it goes to the central nervous system. The thicker branch is the dendron, structurally resembling other long nerve fibers that are axons. This branch courses over a peripheral nerve to its sensory nerve ending. The thickness of the ganglion cell process is roughly proportional to the diameter of the cell body. Large cells have thick myelinated proc-

Each ganglion is enclosed by dense fibrous connective tissue, its epineurium and perineurium. Septa of connective tissue convey blood vessels and lymphatics into the ganglion. The nerve cells tend to be arranged about the periphery as well as in clusters more deeply placed among fascicles of nerve fibers.
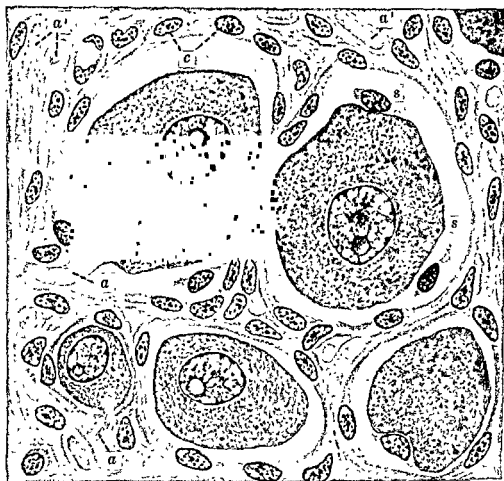
FIGURE 128 Spinal ganglion cells surrounded by neurolemma capsules, *c*, and connective tissue, *s*, capsule cells that appear to be detached and are sometimes called satellites; *a*, axons. Note the axon hillock in a neuron at the upper left. Nissl stain 900 ×.

The nerve cells, called **ganglion cells,** are globoidal and unipolar in most ganglia of this type (Fig. 128). In the vestibular and cochlear cranial ganglia, they are bipolar (Fig. 117). Ganglion cells vary from about 20 to 100 μ in diameter. Each cell is surrounded by a **capsule** which is formed by a prolongation of the neurolemma sheath of its process. This capsule is made up of neurolemma cells often presenting a syncytial appearance. It may have loose or separate cells beneath it (Fig. 128).

FIGURE 131. Autonomic ganglion cells: *c*, capsule, *d*, dendrons of ganglion cells; *p*, preganglionic fibers in the intercellular plexus. Note the pigment in the ganglion cells Silver stain. 900 ×.

form synapses. The axon of an autonomic ganglion cell usually arises from one of the dendrons. It is very difficult to differentiate an axon from other processes, all of which are unmyelinated (Fig. 131). Axons

esses; small cells, thin unmyelinated processes. The unmyelinated processes outnumber the myelinated processes in the spinal ganglia about three to one.

A ratio of one nerve cell to every nerve fiber has been found in the spinal nerve root. No synapses have been observed in cranial or spinal ganglia.

Elsewhere in the body there are ganglia of a different type. These are the **sympathetic** or **autonomic ganglia**. They occur as swellings on the
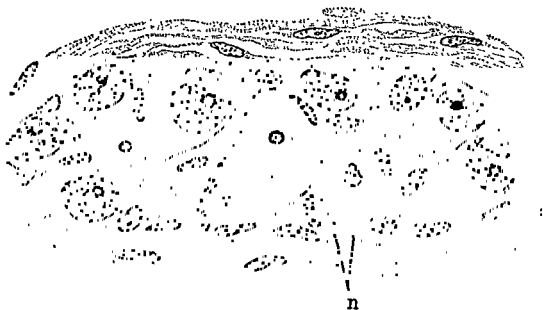
FIGURE 130. *Small autonomic ganglion, showing eight ganglion cells: n, small myelinated nerve fibers of preganglionic type, v, venule. 600 ×.*

sympathetic nerve trunk of the neck, thorax, and abdomen, as well as in association with the splanchnic nerves and several of the cranial nerves. Furthermore, many small accumulations of autonomic ganglion cells are found in the root of the lung, on the heart, and in the walls of the stomach, intestine, and bladder, as well as in other viscera.

All the autonomic ganglia are made up of nerve cells, connective tissue, blood vessels, lymphatics, and nerve fibers, but they differ notably in appearance from spinal ganglia. The ganglion cells are multipolar. Each has numerous dendrons, which branch in the vicinity of the cell body and often become entangled with those of adjacent ganglion cells. Double or triple dendron skeins are thus formed; the cells with these may be enclosed in a common neurolemma capsule. The dendrons of other ganglion cells ramify outside their capsules in the intercellular fiber plexus, which contains also the terminations of nerve fibers entering the ganglion to

many muscle fibers. As many as 120 muscle fibers in the leg muscles are
supplied by one neuron.

The myelinated nerve fiber branches repeatedly as it enters its muscle
fascicle. Each terminal branch takes part in forming one **motor end plate**
on one muscle fiber, as indicated in Fig. 132A. The axis cylinder pierces
the sarcolemma. The myelin sheath terminates by constricting, as at a
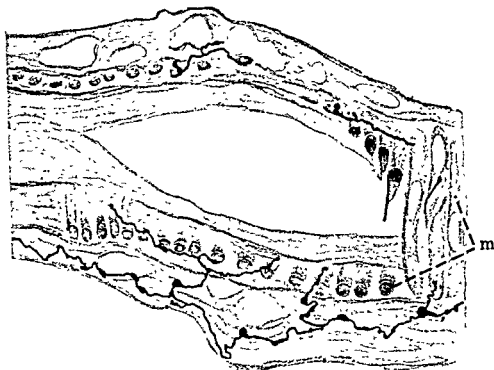
FIGURE 133 Efferent nerve endings on smooth-muscle fibers of an arte-
riole m, smooth muscle. From Olof Larsell, *Anatomy of the Nervous Sys-
tem,* Appleton-Century-Crofts, 1942.

node The neurolemma appears to become continuous with the sarco-
lemma, and the investment of endoneurium joins the endomysium. The
actual nerve ending is thus hypolemmal, *i.e.,* beneath the sarcolemma
The end of the axis cylinder executes a small series of branches and loops
in which the neurofibrils fray out, as seen in Fig. 132B A group of muscle
nuclei in a pool of nonfibrillar sarcoplasm forms a nest, the **sole** of the
motor end plate on which the ending comes to lie.

End organs of much less complexity occur in smooth muscle. They are
formed by the terminations of unmyelinated nerve fibers arising as axons
of the multipolar cells of autonomic ganglia. Each nerve fiber supplies an
unknown number of muscle fibers. The vasomotor fibers to smooth muscle

leave the ganglia in small nerves, which supply smooth muscle, blood vessels, and glands of the viscera, or they join spinal nerves to be distributed to blood vessels, sweat glands, and smooth muscle of hair follicles.
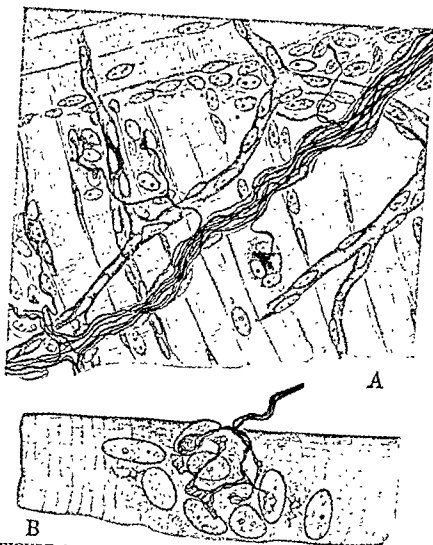
FIGURE 132. Motor nerve endings on skeletal-muscle fibers of a kitten's tongue. Silver stain. A, 400 ×, B, 1200 ×.

EFFECTOR ENDINGS

The motor control of skeletal muscles is effected by impulses conducted over neurons whose cell bodies lie in the spinal cord and brain and whose axons run out in spinal and cranial nerves. One nerve fiber supplies one or two muscle fibers in some of the precisely acting small muscles, such as those moving the eyes. The usual arrangement is one nerve fiber to

RECEPTOR ENDINGS

The long peripheral nerve fibers arising from cranial and spinal ganglion cells end in epithelium, muscle, and connective tissue in many regions. Some end superficially; others, deeply within the body. A great variety of receptor endings is formed by them, but we know little about the functions of many of these, and space does not permit description of all of them. They may be classified in several ways according to whether they are encapsulated, what tissue they associate with, or what general category of functions they serve.

A functional classification divides receptor endings into three main groups. Those which are stimulated by changes in the internal environment are the **interoceptive** endings. Those which tell of degrees of tension, pressure, and orientation are the **proprioceptive** endings. Changes in the external environment are registered by the **exteroceptive** end organs We are acutely aware of the messages initiated by the exteroceptive, which include the visual, auditory, touch, pain, and temperature endings. Proprioceptive endings are concerned with more automatic functions, although we do perceive some deep pressure and are aware of the position of our members. Rarely do we become conscious of the messages received by the interoceptive, visceral endings.

Interoceptive endings· Interoceptive endings are formed by rather simple terminal arborizations of nerve fibers of a number of sizes, in the walls of some of the hollow organs and blood vessels. Many of the free endings in deeper parts of the body belong to this group. Examples of interoceptive endings are the chemoreceptors in the carotid body (page 151) Others are the pressor receptors in the adventitia of the carotid sinus and in other large blood vessels. Figure 135 illustrates one of the latter type. Taste and smell may be considered special varieties of interoceptive sensation. Their endings are described on pages 264 and 341.

Proprioceptive endings: These occur in muscles, tendons, joints, and deep fibrous connective-tissue layers. Three examples are the muscle spindle, the tendon spindle, and the lamellated corpuscle (Pacini). The special endings of the vestibular nerve belong in this category. They are described on page 235.

Muscle spindles are complicated endings occurring in skeletal muscles. As mentioned previously (page 121), a group of muscle fibers of smaller caliber than the working muscle fibers becomes encapsulated in a thin layer of fibrous connective tissue (Fig. 136). These skeletal-muscle

of blood vessels course in the connective tissue of the tunica adventitia, forming a plexus of varying complexity. Here and there individual fibers end on smooth-muscle fibers in delicate rings and minute swellings (Fig. 133). Smooth-muscle innervation elsewhere is similar.

FIGURE 134. Efferent nerve endings on A, cardiac muscle, and B, serous gland acini; n, nerve fibers. Silver stain. 600 ×.

Nerve endings on muscles of the heart are just like those on smooth muscle but are even fewer in number (Fig. 134A). Finally, some glandular epithelium is supplied with secretory nerve fibers whose endings ramify upon and among the cells of the gland (Fig. 134B).

which is found in deep fibrous connective-tissue layers of the skin, around the viscera, in the peritoneum, and in many other places. The corpuscles
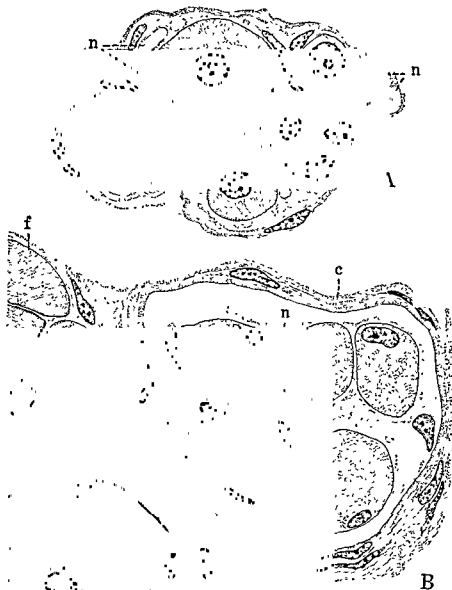
FIGURE 136. Two muscle spindles in cross sections of a cat's gastroc-nemius muscle· A, thinly encapsulated spindle with poorly formed mus-cle fibers, B, more highly differentiated spindle, c, capsule of the muscle spindle, f, working muscle fibers, n, nerve fibers

are very large. Some of them measure 3 or 4 mm. in length and are easily visible to the naked eye. Lamellated corpuscles consist of many concen-trically arranged layers of connective-tissue fibers and cells with consid-erable interstitial fluid between each layer (Fig. 137). This onion-like

spindles are of considerable size, measuring from 2 to 4 mm. in length. Each is supplied by one or more, commonly two or three, myelinated nerve fibers, which terminate after piercing the capsule and form a number of fine branches with little varicosities on them. The latter are applied to muscle fibers of the spindle. Sometimes the endings are arranged ribbon-like about the muscle fibers. Small motor end plates are found on
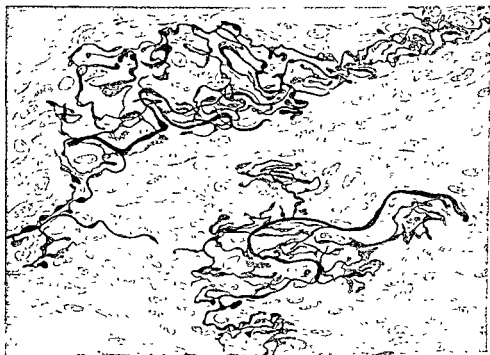
FIGURE 135. Interoceptive nerve ending in the subendothelial layer of the superior vena cava of an adult cat. Silver stain. 300 ×.

the spindle muscle fibers. They are supplied by an additional myelinated nerve fiber. When the working muscle contracts, its spindle muscle fibers contract, too. Their contraction stimulates the sensory endings wrapped about them.

Tendon spindles occur near the junction of muscles and tendons and also in other dense fibrous connective tissue (fascia). They, too, are lightly encapsulated end organs containing ramifications of myelinated nerve fibers. Some are much like those in muscle spindles. Others form palisades among the tendon fibers. Tendon spindles are shorter than muscle spindles, measuring approximately 1.35 mm. in length. Stretching the tendon or pulling on the fascial investments by muscles stimulates these end organs.

Other types of nerve endings occur in muscles, tendons, and fascia. Among these, the most striking is the **lamellated corpuscle** (Pacini)

bulb has a core called the inner bulb, which is penetrated by the axis cylinder of a nerve fiber. The nerve fiber gives up its myelin sheath just outside of the bulb, and occasionally a small branch is formed, which accompanies the main branch into the inner bulb to end there. The corpuscles are stimulated by pressure.

Exteroceptive endings: Many different kinds of nerve endings record changes in the external environment. Visual and auditory functions involve special exteroceptive endings which will be considered with the histology of the eye and ear in Chap. 15. Other exteroceptive functions are served by the end organs for pain, touch, and temperature.

Painful afferent impulses are initiated in **free nerve endings.** Many of the small myelinated and unmyelinated nerve fibers of sensory nerves terminate in very simple free endings in epithelium and connective tissue. These endings are not confined to the superficial structures of the body. They are the most widely distributed of all nerve endings, occurring even in the walls of blood vessels and in the viscera, where pain may be perceived on occasion. In the epidermis, the free nerve endings are confined to the germinative stratum. Figure 138A illustrates their appearance in this location. It is noteworthy that certain regions of the body are sensitive only to pain. One example is the cornea of the eye; another is the tooth pulp. There the only type of nerve ending present is the free nerve ending.

Tactile nerve endings of several types occur in the skin. One of the most sensitive is formed by terminal nerve arborizations in the outer root sheath of a hair follicle. This type of nerve ending, illustrated in Fig 138C, with its hair constitutes a very delicate receptor organ for light touch.

Other little disc-like nerve endings, likewise responding to light touch, occur about special epithelial cells in the germinative stratum of the epidermis. These are the **tactile discs** (Merkel), illustrated in Fig. 138B.

The most highly specialized touch organs are the **tactile corpuscles** (Meisner) which are found in the papillae of the corium of the skin, especially the skin on the volar surface of the fingers and toes (Fig. 138D). These tactile corpuscles are formed by a number of layers of special connective-tissue cells lying transverse to the long axis of the corpuscle. The special connective-tissue cells are encapsulated by a small amount of fibrous connective tissue to complete the tactile corpuscle. A myelinated nerve fiber, upon entering the corpuscle, gives up its sheath, and terminal
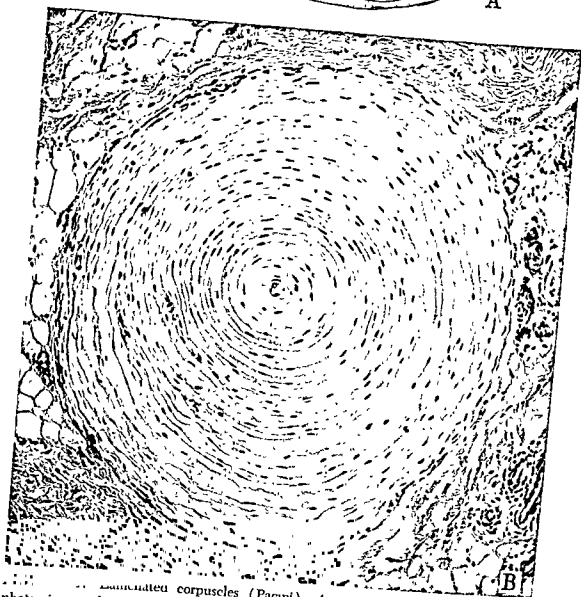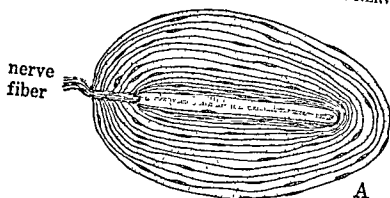
Lamellated corpuscles (Pacini). A, semidiagrammatic drawing; B, photomicrograph of a corpuscle in the human labia majora.

branches ramify among the special connective-tissue cells. Corpuscles of this type are fairly large, measuring from 50 to 100 μ in length.

Lamellated corpuscles (Pacini) in the deep layers of the dermis respond to pressure touch. These are exactly like the lamellated corpuscles that subserve the proprioceptive function.

Endings for warmth and cold have not been identified definitely, and we know very little about them. The two that are usually considered to serve these functions are the corpuscles or **end bulbs of Krause,** thought to be receptors for cold, and the **corpuscles of Ruffini,** possibly responding to warmth. These two types are illustrated in Figs. 138F and E.

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   Here you will find described and pictured certain newly discovered constituents of nerve fibers.

FIGURE 138. Exteroceptive nerve endings (semidiagrammatic): A, free endings in the stratum germinativum of epidermis; B, tactile discs (Merkel); C, nerve ending about hair follicle below sebaceous gland; D, tactile corpuscles (Meisner); E, corpuscle of Ruffini, F, end bulb of Krause. C, E, and F from Larsell, *Anatomy of the Nervous System*, Appleton-Century-Crofts, 1942.

branches ramify among the special connective-tissue cells. Corpuscles of this type are fairly large, measuring from 50 to 100 μ in length.

Lamellated corpuscles (Pacini) in the deep layers of the dermis respond to pressure touch. These are exactly like the lamellated corpuscles that subserve the proprioceptive function.

Endings for warmth and cold have not been identified definitely, and we know very little about them. The two that are usually considered to serve these functions are the corpuscles or **end bulbs of Krause**, thought to be receptors for cold, and the **corpuscles of Ruffini**, possibly responding to warmth. These two types are illustrated in Figs. 138F and E.

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Brain and Spinal Cord

The brain and spinal cord together constitute the central nervous system.[1] They come as close to being composed purely of one tissue, nervous tissue, as any organ. The basic elements of the central nervous system are neurons and neuroglia. Accessories are a closely investing, tough, fibrous connective-tissue membrane, blood vessels, and many macrophages. The macrophages are foreign cells that have been accepted by the family and have become very much at home with the neurons and neuroglia. But the other tissues keep their distance from nervous tissue.

The nervous tissue of the brain and spinal cord is not complex. In fact, it is so simple that there is really very little we can say about the histology of these organs. However, the organization of neurons is extraordinarily complex, and a considerable amount of time must be devoted to its study. Therefore, it is necessary to leave the microscopical anatomy of the brain and spinal cord to another course.

The tissue of the central nervous system is very soft. Lacking collagenous and reticular fibers to hold its elements together, the unfixed brain would be nearly formless were it not for its enveloping membrane and for the penetrating network of blood vessels. These structures form a container for the brain and a skeleton upon which the nervous tissue is hung.

Neurons of the central nervous system are arranged in groups or layers, and their long axons, myelinated and unmyelinated, course from place to place in tracts. Interspersed among nerve cells and fibers all through the central nervous system are the neuroglia.

[1] The optic nerve, retina, posterior lobe of the hypophysis, and pineal body are specialized portions of the central nervous system.

NEUROGLIA

The **neuroglia**, also spoken of as **glia**, are misleadingly called the sup-
porting tissue of the central nervous system. They certainly do not pro-
vide much structural support, and it is doubtful if that is their true func-
tion. More likely, they form a delicate packing material *to hold neurons*
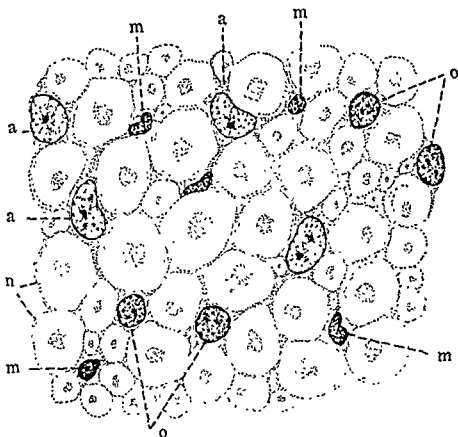
FIGURE 139 Nuclei of neuroglia among myelinated nerve fibers of the
spinal cord: *a*, astrocytes, *m*, microglia (macrophages), *n*, nerve fibers; *o*,
oligodendrocytes. Nissl stain 1200 ×.

apart. Some of them build a barrier against the fibrous connective tissue
of blood vessels and the membrane, pia mater.

Neuroglia are of three distinctly different types: astrocytes, oligoden-
drocytes, and ependymal cells. Each of these varies in appearance in dif-
ferent locations. All forms can be seen in hematoxylin and eosin prepara-
tions of the brain, although details of cytoplasmic structure are lacking.
One must depend upon nuclear differences to tell them apart (Fig. 139).
A number of special staining methods have been devised, and we owe
most of our knowledge of the glia to the use of these.

Astrocytes, as the name implies, are star-shaped cells. They have many branches radiating about equidistantly. They are recognizable by relatively large, pale, ovoid nuclei (Fig. 139). Special methods reveal delicate fibrils in the cytoplasm of some of them, around the nucleus, and
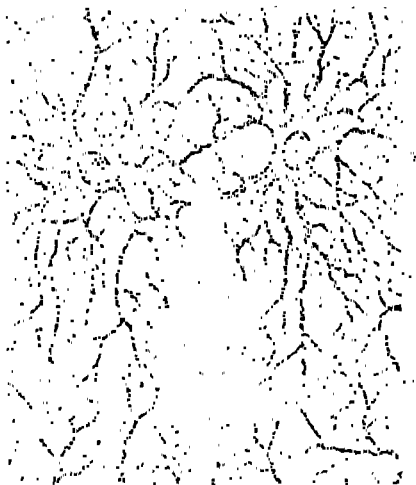
FIGURE 140. Two protoplasmic astrocytes in the cerebral cortex: *m*, macrophage nucleus; *n*, nerve cell; *o*, oligodendrocyte nucleus Special glia stain. 1200 ×.

extending out into the processes. The fibrils resemble those which have been observed in the cytoplasm of fibroblasts. Many astrocytes lack fibrils, and some have them in a few processes only. Those with them are called **fibrous astrocytes;** those without them, **protoplasmic astrocytes.** The fibrous astrocytes are more prevalent among nerve fibers of the tracts. The protoplasmic astrocytes are more numerous in the gray matter with the nerve cells. Special forms develop in the posterior lobe of the hypophysis, the pineal body, and the retina. Those of the brain are illustrated in Figs. 140 and 141.

Fibrous and protoplasmic astrocytes have a common structural feature of great importance. One or two of their processes are stouter than the rest and terminate in little expansions called foot plates. These are applied to the outer connective tissue of blood vessels (Fig. 141) and to the
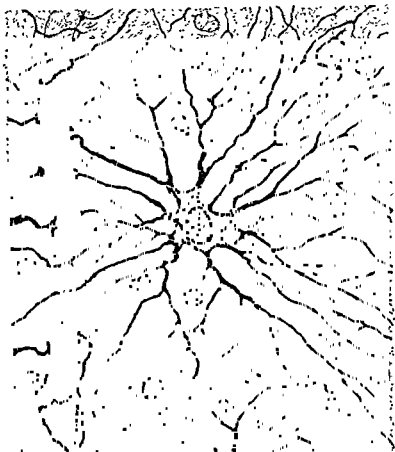
FIGURE 141. Fibrous astrocyte in the white matter of the brain. Note the attachment of two processes by foot plates to the wall of a small blood vessel, *v*. Other foot plates can be seen. Special glia stain. 1200 ×.

fibrous pia mater covering the central nervous system. They form a delicate continuous **glial membrane** about these structures, walling them off from nervous tissue. The perivascular glial membrane and the external glial membrane are, in some unknown way, successful in preventing the encroachment of fibroblast cells. After traumatic injury and other forms of destruction of brain tissue, the fibrous astrocytes take part in building glial scars. In doing so, they wall off fibroblasts and their collagenous fibers.

Oligodendrocytes are smaller than astrocytes (Fig. 142). Their nuclei

usually appear a little darker and are more rounded. It is exceedingly difficult to stain their cytoplasm, which is scanty and extends out in a few thin, sparsely branched processes. These neuroglia often appear in groups around the cell bodies of large neurons, where they are referred to as satellite cells. In the tracts of nerve fibers, oligodendrocytes tend to line up in rows parallel to the fibers. We know very little about them. They take no part in forming the delicate limiting glial membranes; they have no foot plates.
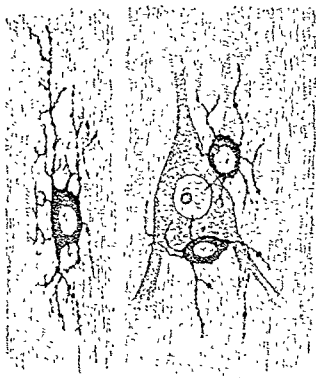
FIGURE 142. Oligodendrocytes in the white matter (left) and gray matter (right) of the brain. Note their proximity to a nerve cell. Special glia stain. 1200 ×.

Ependymal cells line the ventricular system of the brain and spinal cord. They are the direct descendants of the embryonic neural epithelium that formed the primitive neural tube. In routine preparations, ependymal cells look like simple columnar epithelium (Fig. 143). Cilia may be seen on their exposed surface in some places. Fibrils have been demonstrated in the cytoplasm and in the one process that usually projects into the deeper tissue from the base. In places where pia mater is not too far away, these processes take part in the formation of the glial membrane beneath it Ependymal cells appear to be related to the astrocytes.

Ependymal cells have undergone modifications in a few places. They form the low columnar epithelium of the **chorioid plexuses** and somewhat similar epithelium in nonvisual parts of the retina (Chap. 15). The chorioid plexuses dip into the brain ventricles, as illustrated in Fig. 144. The epithelium is extensively invaginated by blood vessels from the pia mater.

There are four chorioid plexuses. They are the main source of the **cerebrospinal fluid** that fills the ventricles and the space between the pia mater and arachnoid membranes to form

the central nervous system. Just how the fluid is formed, whether by transudation from the blood or by secretory activity of the chorioid cells, is not known. About 100 cc. of the fluid is present in the spaces. A mechanism for its return to the blood stream is found in the **arachnoidal villi**. These are thin endothelium-covered connective-tissue fingers that invaginate the large cranial venous sinuses. Cerebrospinal fluid pressure is less than capillary blood pressure in the chorioid plexuses but greater than the venous pressure in the sinuses.

FIGURE 143. Ependymal cells lining the central canal of a human spinal cord. Note cilia on their surface, and processes extending into the gray matter from the bases of the cells. Hematoxylin stain. Photomicrograph, 1200 ×.
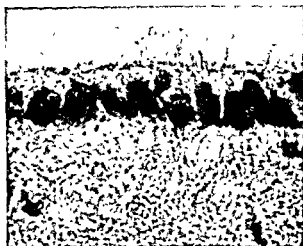
MACROPHAGES OF THE CENTRAL NERVOUS SYSTEM

The macrophages of the brain are misnamed **microglia** or **mesoglia**. They are similar to macrophages of connective tissue, although some are much smaller. Their small dark irregularly shaped nuclei can be identified in ordinary sections (Fig. 139). By special silver methods, it is possible to stain their cytoplasm. They are found with outstretched protoplasmic processes among nerve cells and nerve fibers, like inactive phagocytic cells elsewhere (Fig. 145). Most of the time they have nothing to do. During inflammatory processes and infections and after other injuries of brain substance, they become activated and appear as more compact cells, whose cytoplasm is filled with phagocytized materials. Under these circumstances, lymphocytes, a major source of the macrophages, mobilize in and around the blood vessels of the brain.

NEURONS OF THE CENTRAL NERVOUS SYSTEM

In the preceding chapter, we considered the minute anatomy of neurons, mentioning the great variety of shapes and sizes of nerve cells and calling attention to their interrelations. The difference between those of the brain and those of the peripheral ganglia and nerves is not one of

fundamental intrinsic structure. Aside from their much greater variety—there are only three types of nerve cells in the peripheral nervous system—nerve cells of the brain and spinal cord differ from the peripheral neurons in their organization, interrelations with each other, and relationship to other kinds of cells.

The histological structure of three different parts of the central nervous system is illustrated in Figs. 146 to 148. The spinal cord, cerebellar cortex,

FIGURE 144. Chorioid plexus of the fourth brain ventricle of a monkey; thick section. Nissl stain. Photomicrograph, 150 ×.

and cerebrum are chosen because they differ so widely from each other. It would be misleading to declare that they demonstrate representative structural arrangements. Each is representative of only a particular section of the central nervous system.

The study of the organization of nerve cells into groups, strata, and centers constitutes neuroanatomy. We cannot go into that but point out simply that neurons of one type and general functional similarity tend to be associated. Closely circumscribed groups of nerve cells or nerve fibers generally perform some one specific function. Large masses or diffuse arrangements have less specific functions. The motor nerve nuclei[2] are good examples of closely circumscribed groups. The gray matter of the cerebrum illustrates a more diffuse arrangement. Specific tracts of sensory nerve fibers in the spinal cord and the diffuse layers of nerve fibers in the cerebrum are other examples of this difference.

[2] Nucleus is a term here used to designate a collection of structurally or functionally similar nerve cell bodies in the central nervous system.

In the more circumscribed neuron groups or centers, synapses are arranged to provide great specificity of response. In some of the widely spread strata of neurons, such as the cerebellar cortex, connections are duplicated and reduplicated to provide a broadside or avalanche type of activity. In many places it is possible to perceive an organization that favors continuous conduction in circuits. Some of these circuits are ex-
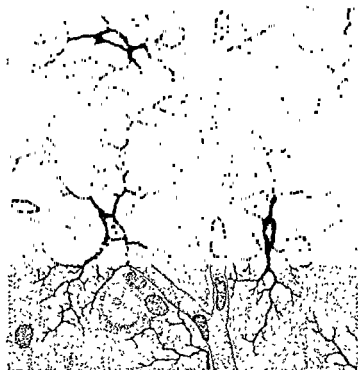
FIGURE 145. Three microglia in the gray matter of the brain. Capillaries, nerve cells, and nuclei of neuroglia may be seen in the background. 1200 ×.

traordinarily complex. Reverberating neuron circuits provide mechanisms for complex activity in the central nervous system. The number of neurons in the brain is immense, and the number of interconnections they make, almost infinite. Any attempt to explain such activities as thought and memory on the basis of anatomical patterns must take these facts into consideration.

The peripheral nervous system is very different from the central nervous system. Isolation of units and specificity of function are more characteristic of peripheral ganglia than of cell groups in the spinal cord. No synapses are made in spinal ganglia, and only a few types of synapse occur in the autonomic ganglia; the brain and cord are great synaptic centers. Other structural and functional differences are evident. Nerve
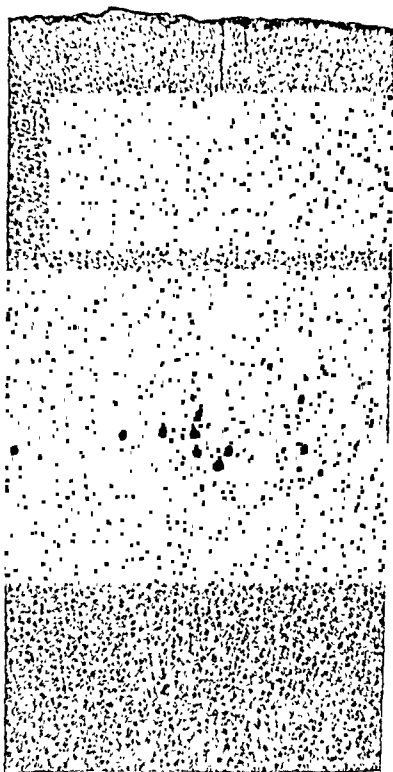
FIGURE 146. Cerebral cortex of a monkey. Nissl stain. Photomicrograph, 80 ×.
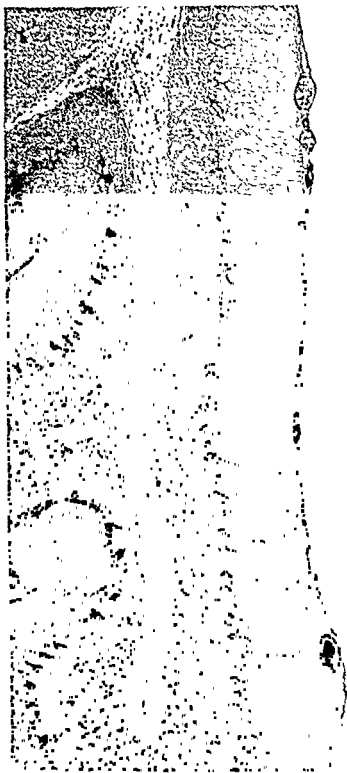
FIGURE 147 Cerebellar cortex of a dog. Silver stain. Photomicrograph, 80 ×.

fibers in the brain and spinal cord lack the cellular sheaths that are characteristic of all those of the peripheral nerves. Neurolemma cells are absent in the central nervous system.

FIGURE 148. Spinal cord of a man. Myelin sheath stain. Photomicrograph, 80 ×.

Fibrous connective tissue separates the elements of the peripheral ganglia and nerve, extending in delicate wisps of endoneurium among nerve fibers and cells. Note that it is kept away from the nerve cell and its axon by the neurolemma cells. Even in the peripheral nerve endings, the

neurolemma guards the axis cylinder right down to its final ramifications. In the brain and spinal cord, fibrous connective tissue is excluded entirely, for it is walled off by perivascular and external glial membranes.

There are many unsolved and baffling problems in the nervous system. Not the least is the enigma of regeneration. Peripheral neurons exhibit this phenomenon. A severed nerve repairs itself by outgrowth of sprouts from the end nearest the nerve cell body. However, the gap between the cut ends must be closed by approximating the ends so that fibrous scar tissue can be excluded from it. In the brain and spinal cord, severed nerve fibers do not regenerate beyond the immediate vicinity of the cut. They too form sprouts, but these fail to show the vigorous directional outgrowth of those in the peripheral nerves.[3]

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   The first nineteen pages are especially appropriate at this time. There is a good collection of illustrations of glia stained by special techniques.

[3] An interesting animated motion picture on the development of the nervous system is available. See Visual Aids, 24.

Membranes of the Brain and Other Organs

A number of fibrous membranes are found in the body which have so much in common that they may well be considered together. All are constructed of fibrous connective tissue and have free surfaces covered with simple squamous epithelium. Some form strong protecting and confining walls. Others, called serous, appear to take part in the formation of fluids which moisten their surfaces under normal physiological conditions or which accumulate in larger quantities under certain disease conditions.

Meninges: It is customary to describe three membranes, or **meninges,** of the central nervous system: the pia mater, arachnoid, and dura mater. Actually, two only are prominent. Only over the spinal cord and in a few places over the brain is the arachnoid a separate membrane. Elsewhere it is fastened to the pia mater, and the two together constitute one soft spongy cushion for the brain.

The **pia mater** proper is composed of fibrous connective tissue containing some elastic fibers. In it are blood vessels and nerves. All the blood vessels are larger than capillaries. They anastomose with one another and give off branches at right angles to the surface of the brain to supply the deep parts of the central nervous system. The pia mater invests the brain and spinal cord very closely, following the various indentations, sulci, and fissures and extending into its substance along the larger vessels for a short distance. It can be stripped away from the brain, because its connective-tissue fibers do not penetrate the brain substance but are walled off by the glial membrane. On its free surface, the pia mater is covered with thin simple squamous epithelium.

The **arachnoid** is a very thin gossamer membrane formed of connective tissue covered on both sides with simple squamous epithelium. It is not vascular. Innumerable delicate strands, or arachnoidal trabeculae, connect it with the surface of the pia mater proper over the brain.

In many ways, it is better to consider the arachnoid simply as the outer part of the pia mater. The pia mater then may be said to be a spongy membrane traversed by larger and smaller fluid-filled and simple squamous-lined spaces. The names **pia-arachnoid** and **leptomeninx** are given to this combined membrane. The spaces in it become wider and form **subarachnoid cisterns** here and there over the brain surface. They coalesce to form the larger **subarachnoid space** of the spinal region.

Apertures in the thin roof of the fourth brain ventricle permit communication with the subarachnoid space. Cerebrospinal fluid is contained in the subarachnoid space, but it is not formed in it. It arises in the chorioid plexuses of the ventricles (page 204) and reaches the subarachnoid space through the apertures of the fourth ventricle.

The **dura mater** is a very tough fibrous connective-tissue membrane (Fig. 149), sometimes called the **pachymeninx**. In the cranium, the outer layer of the dura closely invests the bone and forms its periosteum. The inner surface of the dura mater is covered with simple squamous epithelium. Folds of the inner layer of the dura mater form a number of partial septa, which lie between the major subdivisions of the brain

The membrane is supplied with blood vessels for its own nutrition and contains the large nonmuscular veins, the **venous sinuses**, that drain blood from the brain to the jugular veins of the neck. In the spinal region, the dura mater is separated from the bony vertebral canal by fat and a rich venous plexus.

Nerve roots piercing the dura mater carry investments of its connective tissue, which become the perineurium of the nerve roots. The dura mater becomes continuous with the sheath of the optic nerve and sclera of the eyeball.

There is a capillary space, called the subdural space, between the dura mater and arachnoid. It is moist but contains no significant amount of tissue fluid. The subarachnoid space does not communicate with it Both spaces have slight communication with the lymphatic vessels of the back.

Serous membranes The serous membranes line the peritoneal, pleural, and pericardial cavities. The **peritoneum** of the abdomen is representative It is formed by fibrous connective tissue, over which is a layer of simple squamous epithelium, known as mesothelium The peritoneum

forms a closed cavity[1] and may be divided into a parietal portion, on the body wall, and a visceral portion, reflected over most of the organs in the abdomen. It forms a thin double layer, the **mesentery,** which is attached to the intestines. It also doubles upon itself to form the **omentum.**

The peritoneum consists of fibrous connective tissue of the loose variety in most places, notably in the mesenteries and omentum. There it con-
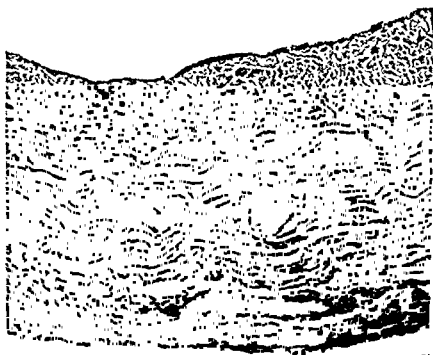
FIGURE 149. Dura mater of a monkey. Photomicrograph, 150 ×.

tains much fat, especially in obese subjects. Over the surface of some of the organs, such as the spleen, its connective tissue is dense and forms the capsule of the organ. The peritoneum of the ovary is a modified type (page 396). The peritoneum is well supplied with blood vessels and lymphatics for its own nutrition and for fat deposition and removal in its areolar tissue. It also carries vessels and nerves for the viscera of the abdomen. Macrophages are numerous in the loose connective tissue of this serous membrane.

The peritoneal cavity, a cleft of capillary thinness, is kept moist by fluid derived from the blood circulating in its membrane; the quantity of this fluid is insignificant in healthy conditions. In it occur a few cells, mostly from the blood.

The omentum presents some features of special interest. The parts of

[1] Uterine tubes provide minute openings into the peritoneal cavity of the female.

it not loaded with fat become quite thin and may be fenestrated. The scanty areolar connective tissue in the omentum is well supplied with capillaries. Macrophages are numerous and may even be found in large clumps, visible to the naked eye and called milk spots. The omentum may play a role in defense of the abdominal cavity against disease.

A small portion of the peritoneal cavity has come to be detached in the male and occupies a position in the scrotum. There the peritoneum forms the **tunica vaginalis** of the testis. Its structure is exactly like that of the peritoneum in the abdominal cavity (Fig. 253).

The **pleura** is a membrane of the thoracic cavities similar to the peritoneum. Its visceral part forms the connective-tissue covering of the lung. It is paved with mesothelium and has more elastic fibers than the peritoneum, especially in its deeper layers. Parietal pleura lines the thoracic cage.

The **pericardium** forms a fibroserous sac for the heart. It is composed of a dense fibrous connective-tissue layer covered by some looser fibrous tissue and the mesothelium. The looser serous layer is reflexed onto the great veins and arteries as they pierce the fibrous layer to enter and leave the heart. The heart is covered by the serous layer of visceral pericardium. The dense fibrous deeper layer of parietal pericardium fuses with the adventitial coat of the great blood vessels and with the central tendon of the diaphragm.

Synovial membranes: Joint cavities are partially lined by synovial membranes resembling the serous membranes of the body cavities. They were described on page 101.

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1. Weed, L. H.: Certain Anatomical and Physiological Aspects of the Meninges and Cerebrospinal Fluid, *Brain*, vol. 58, pp. 383–397, 1935
   This brief review of the subject will provide orientation and give a source of references for further reading.

Visual and Auditory Organs

The special sense organs are receptors concerned with smell, taste, vision, and hearing. Closely associated with the organ of hearing is the vestibular mechanism for balance and orientation. It is more convenient to describe the olfactory and gustatory endings with the nasal cavity and the tongue (pages 339 and 264) than to treat them in this chapter. The receptors for light and sound require special consideration in deference to their very great importance. Far more messages reach your brain from these two groups of receptors than from all the rest of the sensory nerves combined.

EYEBALL

The eye develops as an outpocketing of the forebrain of the embryo. This part of the neural tube forms the inner coat, including the retina of the adult eye. The retina and the optic nerve connecting it with the brain are parts of the central nervous system. Like the rest of the central nervous system, they are covered with vascular and protective fibrous connective-tissue membranes. These coverings, derived from embryonic mesenchyme, are the middle vascular coat, comparable with the pia-arachnoid, and the outer fibrous coat, continuous with the dura mater. Another very important component of the eye, the crystalline lens, arises from the surface ectoderm over the optic vesicle of the embryo. Spaces in front of the lens contain a special tissue fluid known as aqueous humor. Behind the lens is a jelly-like substance, the vitreous body. As in the brain and the spinal cord, there are no true lymphatics in the eyeball.

The eyeball is remarkably like a camera, with its lenses, iris diaphragm, and photosensitive layer of tissue, the retina, in a black pigmented com-

partment. Transparency of the light-transmitting components of the eyeball is one of the visual organ's most extraordinary features. This is not something acquired but is maintained during development. In the early embryo all tissues are transparent. Transparency can be maintained in the
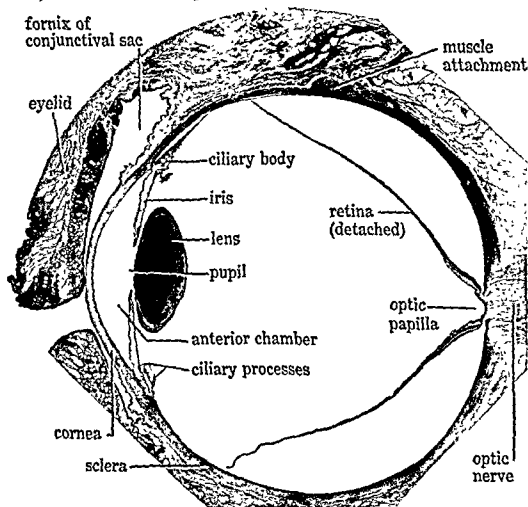
FIGURE 150. Human eyeball and eyelids sectioned sagittally through the pupil and optic papilla. This remarkable specimen was contributed by Dr. L. L. Caulkins. It was removed surgically for carcinoma of the lacrimal gland. Artifactual detachment of the nervous portion of the retina demonstrates the progressive increase in retinal thickness of that layer toward the optic papilla. Photomicrograph, 4 ×.

adult only so long as the lenses are kept properly nourished, protected, and wet.

Outer fibrous coat· The covering of the eye that corresponds to the dura mater is dense fibrous connective tissue, even more compactly arranged than around the brain. This is the layer that gives shape to the globe of the eyeball. Its two parts are the sclera and cornea.

The **sclera** forms the posterior five-sixths of the fibrous coat (Fig. 151). It is perforated behind by optic nerve fibers. There it blends with the fibrous connective-tissue sheath of the optic nerve. In front, it joins the
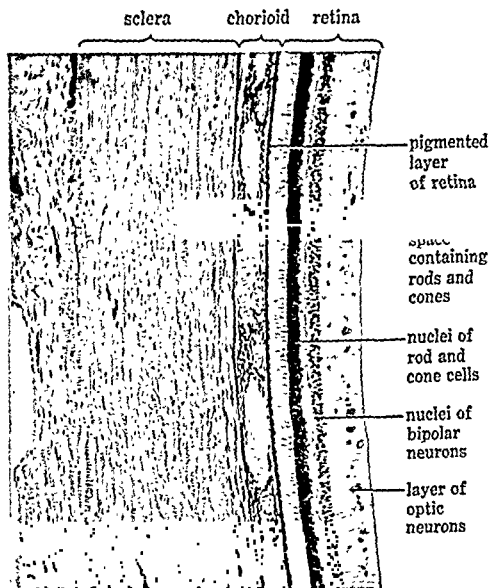
FIGURE 151. Human eyeball. The section passes through all coats about 5 mm behind the ora serrata, exterior is toward the left. Specimen in the Piersol collection. Photomicrograph, 125 ×.

cornea and is covered at the white of the eye by part of the conjunctiva. Externally, it blends with the loose fibrous connective tissue of the orbit. Internally, its cells become pigmented as it joins the vascular coat of the eyeball. At the sclerocorneal junction, it contains a prominent blood vessel, the **venous sinus** of the sclera. Elsewhere, vessels are sparse. To the

sclera are attached muscles that move the eyeball. Through it pass arteries, veins, and nerves.

The **cornea**, forming the anterior one-sixth of the fibrous coat, has a
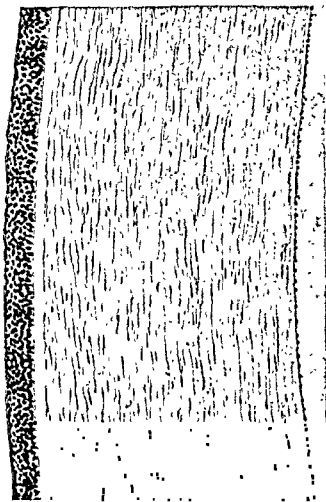
FIGURE 152. Human cornea. The external epithelium and its heavy basement membrane are on the left; the internal, simple epithelium and its basement membrane, on the right Photomicrograph, 125 ×.

stronger curvature than the sclera. This makes it protrude. The cornea is the most important element of the dioptric apparatus It has two and one-half times the refracting power of the crystalline lens.

The transparent, dense, fibrous connective tissue of the cornea is lamellated. In front, it is covered by stratified squamous epithelium, continuous with that of the conjunctiva. In back, it is lined by a single layer of rather thick squamous cells. Very thick homogeneous basement mem-

branes are seen beneath both epithelial layers. There are no blood vessels but many nerve fibers in the cornea. The nerve fibers are unmyelinated,
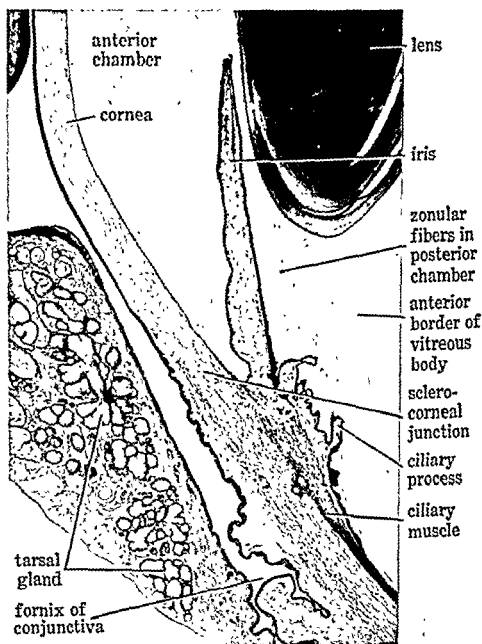
FIGURE 153 Human eye. The specimen is the same as Fig. 150, showing *iris, ciliary body, and other details Photomicrograph, 15 ×.*

and their endings are sensitive only to pain. The structure of the cornea is shown in Fig. 152.

The **sclerocorneal junction** is a transition zone. The outer epithelium becomes thicker. The basement membrane of the inner epithelium

changes into a loose fibrous connective-tissue meshwork, and blood vessels are found in it. It may be seen in Fig. 153.

Middle coat. The middle coat of the eyeball, called the **uvea**, is vascular and contains important smooth muscles. This coat has a stroma of loose fibrous connective tissue firmly adherent to the inner but only loosely attached to the outer coat except at the entrance of the optic nerve and at the sclerocorneal junction. A potential perichorioidal space corresponds, in a way, to the subdural space. Three parts of the middle coat are the chorioid layer, ciliary body, and iris.

The **chorioid layer** lies between the sclera and the retina, extending only as far forward in the eyeball as the ora serrata of the retina. It can be seen in Fig. 151. It is scarcely more than 0.25 mm. thick but contains a rich supply of arterioles and venules. Capillaries form a thin layer internal to the arterioles and venules. A loose fibrous connective-tissue stroma contains pigmented cells. The innermost part of the chorioid layer forms a homogeneous basement membrane for the pigmented epithelium of the retina.

The **ciliary body** extends forward from the ora serrata of the retina to the sclerocorneal junction. It is the thickest portion of the middle coat, roughly triangular in sections. It forms a fibromuscular ring for attachment of the suspensory ligament of the lens. The incomplete perichorioidal space continues forward to separate the ciliary body from the sclera. On the inner side of the ciliary body is an epithelium continuous with the retina. The inner surface is thrown into 70 to 80 radiating folds which are especially prominent at the free mesial edge of the ciliary body. These folds form the **ciliary processes**. In a gross specimen, their appearance is accentuated by the dark pigmentation between them. In front, the ciliary body meets the base of the iris, as seen in Figs. 153 and 154.

The ciliary body contains all the elements of the chorioid except the capillary layer. In addition, a significant amount of smooth muscle is added. This is the **ciliary muscle**, formed of fibers coursing meridionally, radially, and circularly. The principal meridional fibers attach in front to the sclera near the sclerocorneal junction and pass back to insert into the connective tissue of the chorioid layer. The circular fibers form a sphincter at the base of the iris. Radial fibers are disposed between these two groups. The action of the ciliary muscle is to relax tension upon the crystalline lens, permitting it to increase in thickness.

The double layer of low simple columnar epithelium lining the ciliary body is the **pars ciliaris retinae**. Cells adjacent to the stroma are heavily
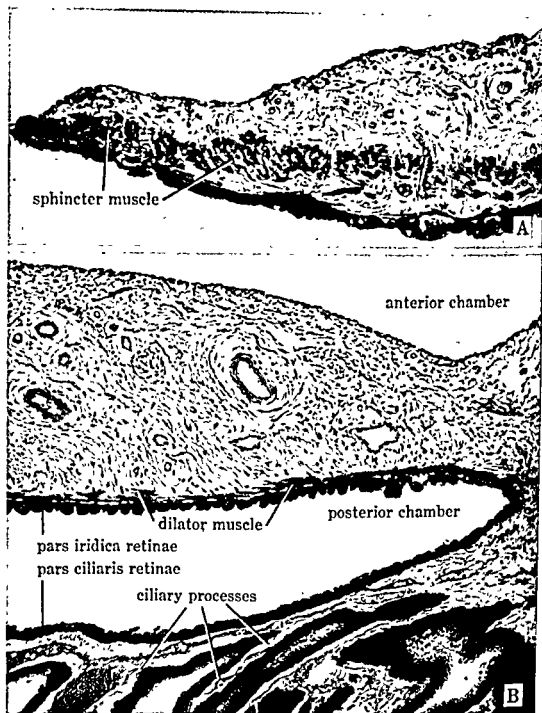
FIGURE 154 Human iris from a blue-eyed subject: A, inner rim of the iris showing its stroma, sphincter muscle, and pigmented epithelium on the posterior surface; B, peripheral one-third of the iris, the posterior chamber, and ciliary processes. Note the arterioles with thick adventitia, the dilator muscle of the iris, and the pigmented epithelium of the pars iridica retinae. Specimen in the Piersol collection. Photomicrographs, 125 ×.

pigmented. The inner layer is made up mainly of nonpigmented cells. A space between the two layers of cells no longer exists in the adult but was present in the embryo.

The **iris** is the most anterior part of the middle coat of the eye. It is a thin annular plate of vascular loose fibrous connective tissue, lined behind by the nonnervous and pigmented **pars iridica retinae**. The forward surface is covered by a simple squamous epithelium, thinner than that backing the cornea. The iris lies in front of the lens, and its aperture, known as the **pupil**, admits light to the visual compartment of the eye.

A **sphincter muscle**, made of circular bands of smooth-muscle fibers, is present in the iris. This contracts the pupil. The **dilator muscle** of the pupil is formed of myoepithelial cells radially arranged and more peripherally placed than the circular fibers. Both muscles may be seen in Fig. 154.

In front of the pupillary muscles, the stroma contains a variable number of pigmented connective-tissue cells. Eye color depends upon their number. When many are present, eyes are brown; when few, they are blue. The absence of all pigment, including that of the pars iridica retinae, occurs in albinos.

Vascular rings are formed by arterioles at the base of the iris and at its inner border near the pupil. Connecting vessels provide a rich blood supply.

Inner coat: The inner coat of the eyeball is the only one derived from the optic vesicle of the embryo. The optic cup, which is formed by invagination of the vesicle, has two layers. The adult derivative of the outer wall of the cup is the pigmented epithelium of the retina. Derivatives of the inner wall of the cup are the nonpigmented epithelium and nervous part of the retina. The pupillary border of the posterior epithelium of the iris represents the lip of the embryonic optic cup.

The two epithelial layers of the retina are easily separable in the adult because a potential **intraretinal space** exists between them. In Fig. 150, the retina has become detached at this space. Into this space extend processes of visual cells and retractable protoplasmic processes of the pigmented epithelial cells. This space is comparable with the ventricles of the brain. Indeed, it contains tissue fluid, albeit in minute quantity.

The **nonnervous part of the retina** has been mentioned in description of the uvea. It begins at the **ora serrata** as a double layer of epithelium running forward over the ciliary processes and over the posterior wall of the iris, where it is called the **pars ciliaris** and the **pars iridica retinae**.

Its darkly pigmented deep layer of cells darkens the interior of the eyeball. Some of the superficial low columnar cells, mainly those on the cili-
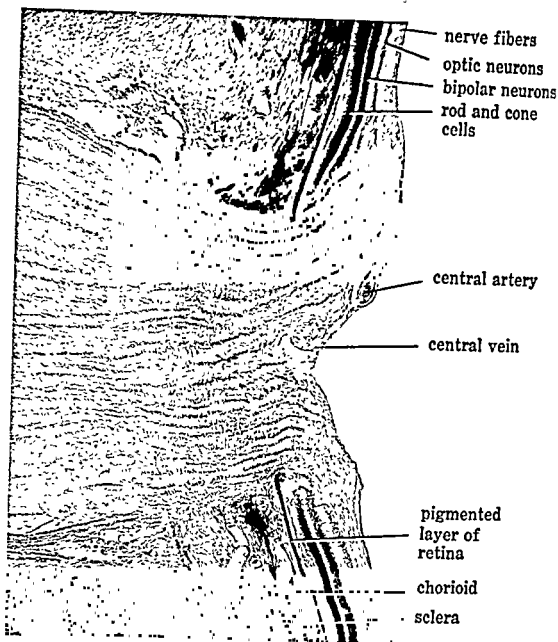
FIGURE 155. Optic papilla and optic nerve of a human eye. Specimen in the Piersol collection Photomicrograph, 40 ×

ary processes, resemble the epithelial cells of the chorioid plexuses of the brain. They form a fluid, the **aqueous humor**, which fills the space in front of the crystalline lens. Aqueous humor finds its way through tissue spaces in front of the base of the iris, passing into the venous sinus of
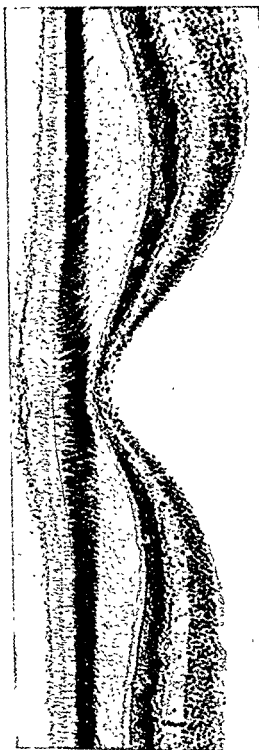
the sclera and other blood vessels. It has much to do with maintaining normal eyeball shape by providing optimum intraocular pressure.

The **pars optica retinae** is composed of the **pigmented layer**, a low, simple columnar epithelium, and the **retina proper**, a thin sheet of nervous tissue. The retina proper is made of neurons and neuroglia, is supplied by blood vessels, and lacks lymphatics. The pars optica is quite thin, measuring only 0.4 mm. at the posterior pole of the eyeball and 0.1 mm. at the ora serrata.

Like central nervous system structures, the nervous layer of the retina is walled off from other tissues by glial membranes. These are the **external limiting membrane** and the **internal limiting membrane**. The cells whose processes form these membranes are modified astrocytes arranged with their long axes at right angles to the retinal surface. The internal limiting membrane is very thin and hard to see and forms the retinal surface that is presented to the vitreous body. The external limiting membrane is more prominent. It borders the intraretinal space.

FIGURE 156. Macula and fovea of a detached human retina. The cones have pulled away from the pigmented epithelium, cleavage taking place in the intraretinal space. Compare the thickness of each layer in the macula with the same layers in Fig. 151. Specimen by Dr. L. L. Caulkins. Photomicrograph, 125 ×

The retina proper, exclusive of its pigmented epithelium, has three distinct layers of nuclei (Fig. 157), belonging to its three principal types of cells, which are **visual cells, bipolar neurons,** and **optic neurons,** misleadingly called ganglion cells.[1] There are also three nonnuclear layers of the retina. Synapses occur in two of them between the visual cells and bipolar neurons and between bipolar neurons and optic neurons. The innermost layer is made up of myelinated axons of the optic neurons, which are converging upon a point about 3 mm. medial to the posterior pole of the eye. There, at the **optic disc** or blind spot, these fibers turn out through perforations in the sclera to form the **optic nerve.** Other retinal elements are lacking at this point, as will be seen in Fig. 155

Near the posterior pole of the eyeball, the retina is thin at a central depression, the **fovea centralis.** Here there are few retinal elements, except the outer part of the visual cells (Fig. 156). The other cells and the nerve fibers are piled up around this depression to form the **macula lutea,** whose thick circular ridge sometimes appears yellowish in the living eye. At the fovea, light can reach the photoreceptors without traversing all the other layers of the retina. Thus, the fovea is the point of greatest visual acuity. All that you view directly and critically is focused onto it.

The **photoreceptors** are of two kinds: the **rod cells** and the **cone cells.** They are neuroepithelial cells whose nuclei and axons lie beneath the external limiting membrane. Their outer, very highly specialized, light-sensitive processes pierce this membrane and lie entirely within the intraretinal space between the external membrane and the pigmented epithelium. These specialized processes of the visual cells are the rods and cones proper (Fig. 157).

Rods are about 60 μ long, twice as long as **cones,** but are only 2 μ thick, while the cones measure about 7 μ in diameter. Each consists of an inner thick and outer thin segment, but the outer segment of the cone is short. In the fovea centralis, the only photoreceptors are cones. Elsewhere, rods are much more numerous than cones, outnumbering them about 20 to 1. Rods serve in dim-light vision; cones are concerned with bright-light and color vision. In bright light, the pigmented epithelial cells extend protoplasmic processes into the intraretinal space among the outer rod segments. These processes retract in dim light and permit more light to reach the rods.

Each cone cell synapses with one bipolar neuron which, in turn, synapses with one optic neuron. Rod cells, on the other hand, are grouped

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[1] Actually there are more than three types of neurons in the retina, but a detailed description has no place in this introductory course in histology.

in relation to their respective bipolar neurons. The macula lutea, containing the nervous elements for the cones of its fovea centralis, gives rise to one-third of all the fibers of the optic nerve. This is remarkable because it is only a small spot, occupying no more than one-twentieth of the retinal area. ──
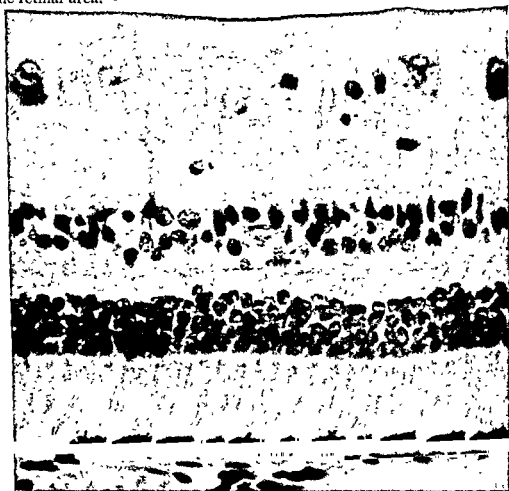
FIGURE 157 Rods and cones of a human retina· a detail from Fig. 151 at higher magnification The upper surface is interior. Photomicrograph 600 ×.

The rods and cones are not supplied directly by blood vessels, for the intraretinal space in which they lie is avascular. Tissue fluid diffuses into this space from the chorioid. The retina has its own blood supply, the **central artery** and **central vein**, which come in through the optic nerve and optic disc. These vessels ramify over the inner surface of the retina and can be observed through the pupil with an ophthalmoscope. Their branches course in such a way that they avoid the fovea centralis. The central artery is a true end artery. It anastomoses with no other artery, and its branches do not anastomose with one another.

Crystalline lens and vitreous body: Light passes through the cornea, aqueous humor of the anterior chamber, crystalline lens, vitreous body, and the layers of the retina to reach the intraretinal space containing the rods and cones. Clear normal vision is maintained only so long as these structures remain transparent. Age may impair their transparency or may discolor them.

The **vitreous body** forms the largest component of the dioptric apparatus. About four-fifths of the eye is made up by it, for it fills the space behind the lens. The vitreous body is made of jelly and is structureless in the living animal. Occasionally a lymphocyte makes its way into it.

The **crystalline lens** is an interesting specialization of epithelium. It begins as a thickening, then an invagination of the surface ectoderm of the embryo. A vesicle is formed which pinches off within the optic cup. Only the posterior wall of the vesicle becomes specialized. The anterior wall remains as a single layer of low columnar or squamous cells. The posterior epithelial cells become enormously tall; in fact, become the **lens fibers**, up to 10 mm. in length and concentrically arranged. The center of the lens is denser than the periphery. It is the oldest part. The soft peripheral portion gradually hardens with age; and, as it does so, the usefulness of the lens in accommodation declines. The lens is enclosed in a transparent homogeneous membrane, the **lens capsule.**

The **suspensory ligament of the lens** is formed of many delicate **zonular fibers** which connect the lens capsule at the periphery, or equator, of the lens with the ciliary processes. These fibers hold the lens under slight tension favorable for focusing images of distant objects onto the retina. The sphincter action of the ciliary muscles during contraction relieves this tension and permits the lens to thicken in consequence of its own elasticity. Thus, images of nearer objects are focused.[2]

CONJUNCTIVA AND ASSOCIATED STRUCTURES

Conjunctiva: The **conjunctiva,** continuous with the skin of the eyelids, is a layer of stratified squamous epithelium of the noncornified variety resting upon a lamina of fibrous connective tissue. In other words, it is a mucous membrane.[3] It lines the **eyelids,** folds back upon itself at the **fornix,** and covers the anterior surface of the eyeball to form an open **conjunctival sac.** These relations are demonstrated in Fig. 158. The con-

[2] For another interpretation, see Visual Aids, 29.
[3] Mucous membranes are described on p 257
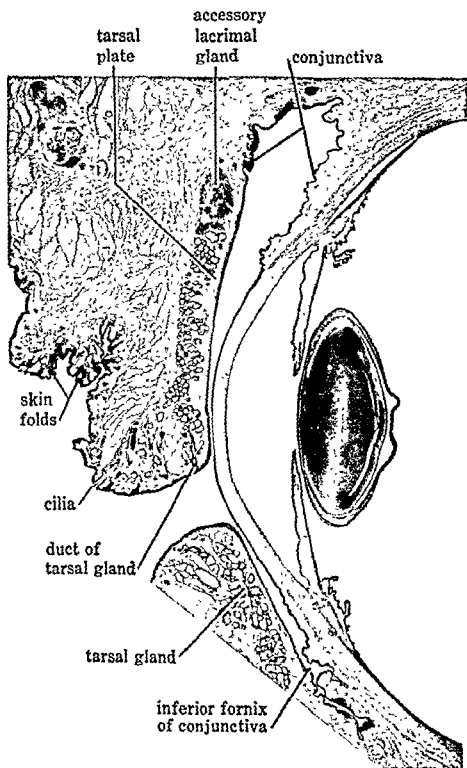
FIGURE 158 Conjunctiva, eyelids, and anterior segment of the eyeball the same specimen as Figs 150 and 152 The dark area in the upper left is a neoplasm Photomicrograph, 7 ×

junctiva is smooth except in the fornix and medially at the lacrimal **caruncle.**

Over the cornea, the epithelium is stratified squamous and is transpar-

FIGURE 159. Human lacrimal gland. The junction of secreting acini with two ducts may be seen. Specimen in the Piersol collection. Photomicrograph, 300 ×.

ent. Over the tarsal plates of the eyelids, it becomes very thin; in places it is reduced to a double layer of cells—in reality, stratified columnar epithelium. Goblet cells may be present in the epithelium of the conjunctival fornix.

The fibrous connective tissue of the conjunctiva binds the epithelium

to the tarsal plates of the eyelids and to the surface of the eyeball. Elsewhere, it is loose and contains lymphocytes. Several tiny tubulo-acinous serous glands lie in the loose connective tissue beneath the conjunctiva,
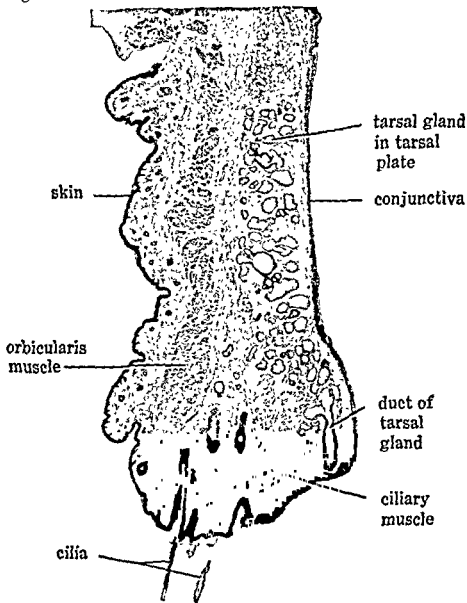
FIGURE 160 Human eyelid. Specimen in the Piersol collection. Photomicrograph, 20 ×.

opening by ducts into the anterior wall of the fornix of the conjunctival sac.

Lacrimal gland: The major gland of the conjunctiva is the **lacrimal gland.** This lies above the eyelid and in the orbit. It opens into the conjunctival sac in front of the superior fornix by 10 to 14 ducts. The

lacrimal gland is a compound tubulo-acinous serous gland which secretes the tears. Figure 159 shows its structure.

A constant flow of secretion provides the conjunctiva and cornea with a film of moisture. Excess secretion is collected at the medial ends of the eyelid margins, where there are two little papillae, each containing an opening of one of the **lacrimal ducts**. These lacrimal ducts, two in number, are lined with stratified squamous epithelium. They empty into the **lacrimal sac**, and the secretion that they carry is ultimately conveyed to the nose by means of the **nasolacrimal duct** (page 341).

Eyelids: These are simply folds of thin skin. They are illustrated in Figs. 158 and 160. A **tarsal plate** of dense fibrous connective tissue gives form to each eyelid. In this plate are embedded branched acinous **tarsal glands** (Meibom), of the holocrine variety. They are modified sebaceous glands (page 252), opening by numerous ducts onto the margins of the eyelids. Their secretion prevents the eyelids from sticking together and helps confine the tears to the conjunctival sac.

Skeletal muscle fibers of the **orbicularis oculi** are prominent in the eyelid. They form a layer in front of the tarsal plate and serve to close the lids. The upper eyelid is raised by action of another muscle, which lies outside of the eyelid in the orbit and whose tendon inserts into the dense fibrous connective tissue of the tarsal plate as well as into the skin. Smooth-muscle fibers, forming the **tarsal muscle** (Müller), occur above the tarsal plate of the upper eyelid.

The edges of the eyelids are bordered by the **eyelashes**, or **cilia**, with their associated glands. These form two or three irregular rows placed close together. They are strong curving hairs whose follicles are buried deeply in the border of the eyelid. The eyelash follicles lack the usual arrector muscles, but they have sebaceous glands. A row of large modified sweat glands, the **ciliary glands** (Moll), is found between the follicles.

EXTERNAL AND MIDDLE EARS

The **external ear** is made up of the auricle and external auditory meatus. The **auricles** are not particularly useful for catching sound waves, but you would look strange without them. Each is formed of thin skin, with scanty and very small sweat glands, over an irregularly shaped plate of elastic cartilage. The auricle opens into a cartilaginous and bony canal, which is the **external auditory meatus**, lined with skin containing apocrine **ceruminous glands** which secrete ear wax.

The **middle ear** is a bony space, which separates the deeply embedded auditory organ proper from the outside world. It consists of the **tympanic cavity** and some irregular air spaces similar to the paranasal sinuses (page 341) but lined by much thinner epithelium. It opens into the nasopharynx by way of the **auditory tube** (Eustachio).

The **tympanic membrane**, or ear drum, separates the middle ear from the external auditory meatus. This is a thin dense fibrous connective-tissue membrane with skin on the outside and simple squamous epithelium on the inside.

Two windows into the bony labyrinth of the inner ear are found on the medial wall of the tympanic cavity. These are not open communications, for the **oval window** adjacent to the vestibule is blocked by bone, and the **round window** is closed by a membrane.

The **auditory ossicles** bridge the tympanic cavity from the tympanic membrane to the oval window. They are three tiny bones: the **malleus,** partly embedded in the tympanic membrane; the **stapes** whose base fits into the oval window; and a third ossicle, the **incus,** connecting the other two. The ossicles are covered with a layer of fibrous connective tissue and simple epithelium continuous with the lining of the tympanic cavity. Vibrations of the tympanic membrane can be transmitted by the ossicles to the internal ear.[4]

INTERNAL EAR

A series of oddly shaped channels in the particularly hard petrous part of the temporal bone comprises the **osseus labyrinth.** Like all bone, the channels are lined with periosteum, through which blood vessels and nerves can pass. In most places, some looser fibrous connective tissue lies over the periosteum, and this has spaces containing a special tissue fluid, the **perilymph.** These spaces and the perilymph are homologous with the subarachnoid space and its cerebrospinal fluid. They are lined with simple squamous epithelium.

Suspended in the bony labyrinth by trabeculae that convey blood vessels, and cushioned from the bony labyrinth by perilymph, is a similarly shaped system of fibrous tubes and sacs. This is the **membranous labyrinth.** It is lined with epithelium and contains another clear fluid, the **endolymph.** The bony labyrinth is deficient at the oval and round windows, which are closed by the stapes and a fibrous membrane. The mem-

4 See Visual Aids, 30

branous labyrinth does not come into such close association with the middle ear. All parts of the membranous labyrinth intercommunicate, but no part communicates with any other space.

The epithelial lining is derived from the embryonic ectodermal otic vesicle. Textbooks of embryology tell the fascinating story of development of the membranous labyrinths from ectodermal primordia.
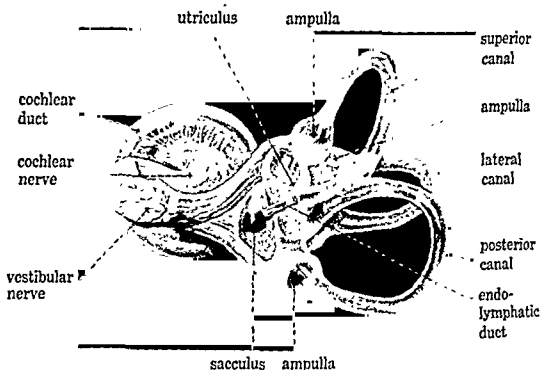
FIGURE 161. Model of human membranous labyrinth. From W. Spalteholz, *Handatlas der Anatomie des Menschen*, 10th ed., S. Hirzel, Leipzig, 1921.

The term membranous labyrinth is not synonymous with organ of hearing but refers to the system of tubes and vesicles in which the vestibular as well as the auditory sensory receptors are located. The only part concerned with hearing is the **cochlear duct**. The rest is for balance and orientation. Subdivisions of the membranous labyrinth are the three **semicircular canals** with **ampullae**; the **utriculus**, into which the semicircular canals and ampullae open; the **sacculus**, interposed between the utriculus and the cochlear duct; and the narrow interconnecting channels, including a terminal dilatation of one of them which is the **endolymphatic sac**. The semicircular canals occupy separate bony channels in three spatial planes. The utriculus and sacculus together occupy the one bony vestibule. The relationships of these various subdivisions of the membranous labyrinth are illustrated in Fig. 161.

Vestibular part of the labyrinth: The walls of the sacculus, utriculus, and semicircular canals are structurally alike. They are dense fibrous connective tissue lined with simple squamous epithelium except in regions where patches of special neuroepithelium occur. One such patch is found in each ampulla, one in the sacculus, and one in the utriculus. The sensory areas of the ampullae are the **cristae**, little ridges placed transverse to the long axis of the canal. The sensory areas of the sacculus and
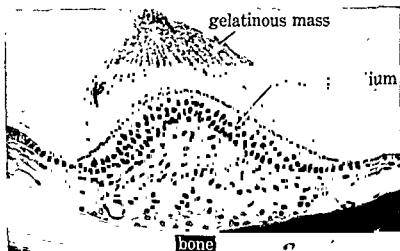
FIGURE 162. Ampullary crista of the posterior semicircular canal; guinea pig labyrinth. The gelatinous mass containing processes of hair cells has shrunk in fixation of the tissues. Photomicrograph, 90 ×.

utriculus are called **maculae**. All have similar structure, as illustrated in Figs. 162 and 163.

The wall of the labyrinth is locally thickened at the cristae and maculae. The epithelium increases in height, becomes columnar and then pseudostratified, and rests upon a basement membrane. Among the tall columnar cells are some short ones located at the surface of the epithelium. These do not reach the basement membrane. They have tufts of long nonmotile cilia, giving them the name **hair cells**. The tufts of cilia extend into the endolymph and support a layer of gelatinous substance on their tips. In the maculae, this is the **otolithic membrane**. It has little crystalline particles embedded in it which are called **otoconia**. The ciliary tufts of the cristae are covered by a thin gelatinous substance.

The subjacent fibrous connective tissue is thickened and contains vestibular nerve fibers. These pierce the basement membrane, and their terminations ramify around the bases of the hair cells. Stimulation of the

hair cells by movement of the head or changing its position initiates nerve impulses.

Cochlea: The auditory part of the bony labyrinth is the **cochlea**. It is a spiral channel about 6 cm. long which makes two and one-half turns in man. When viewed in mesial section from base to apex, as in Fig. 164, a central bony stalk, the **modiolus**, will be seen. A spiral shelf of bone winds up the modiolus like spiral stairs around a central pillar. This **osseous spiral lamina** partly subdivides the bony cochlea.
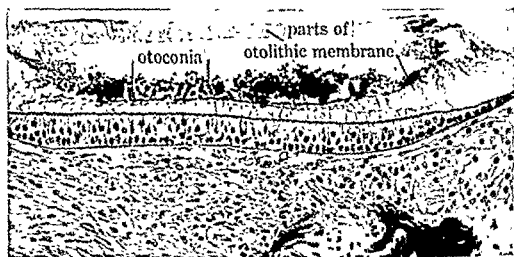
FIGURE 163. Macula of the utricle; guinea p   ... 'ne otolithic membrane has been deformed in preservation of the tissues, otoconia are present. Photomicrograph, 90 ×.

Like other parts of the bony labyrinth, the cochlea is lined with fibrous connective tissue forming its periosteum. This varies in thickness on different parts of the cochlear wall. It is especially thick, spongy, and vascular on the outer wall, where it is called the **spiral ligament**.

The **cochlear duct** is the membranous labyrinth of the cochlea. It has blind ends but communicates at its lower turn with the sacculus by a little tube, the **ductus reuniens**. Through this, the endolymph of the cochlear duct may pass into the membranous vestibular labyrinth. The cochlear duct is a fibrous connective-tissue tube lined with epithelium, some of which is neuroepithelium. In this respect, it resembles other parts of the membranous labyrinth. But here the similarity ends, for the cochlear duct has become remarkably specialized.

Instead of being loosely suspended in the bony labyrinth by trabeculae of fibrous connective tissue, as is the case of the vestibular labyrinth, the cochlear duct is fused with the spiral ligament on the outside and with

the osseous spiral lamina internally. These attachments cause it to assume a triangular shape in cross section. The connective tissue of its upper wall is very thin. That of its lower wall is very stout and forms the **basilar membrane** which is stretched between spiral ligament and osseous spiral lamina. The basilar membrane is a ribbon of dense fibrous connective tissue. As is clearly seen in Fig. 164, it is narrowest in the

FIGURE 164 Human cochlea sectioned through the modiolus· *b*, basilar membrane (compare width in lower and upper turns); *c*, cochlear duct, *g*, spiral ganglion; *l*, spiral ligament, *n*, cochlear nerve bundles, *o*, osseous spiral lamina; *t*, scala tympani; *v*, scala vestibuli. Connective-tissue stain. Specimen by Dr. Harold Koenig Photomicrograph, 15 ×

lower turn and widest in the upper turn of the cochlea. It contains cross fibers of progressively increasing length, the **auditory strings,** and may well be thought of as comparable to a harp.

The thin upper wall of the cochlear duct is lined with simple squamous epithelium and is called the **vestibular membrane** (Reissner). The spongy outer wall, which attaches to the spiral ligament, is lined by pseudostratified epithelium forming the **stria vascularis,** so called because it contains capillaries from the subjacent connective tissue.[5] The epithelium of the basal wall of the cochlear duct is columnar but presents a

[5] This is an exception to the rule that there are no blood vessels in epithelia.

most remarkable appearance where it is adapted to receive vibrations and translate them into nerve impulses. There it forms the spiral organ.

The **spiral organ** (Corti) is a complex arrangement of tall supporting cells, resting upon the basilar membrane, and short hair cells with cilia, upon the tips of which rests a delicate **tectorial membrane**. This peculiar filamentous tectorial membrane is derived from more mesially placed
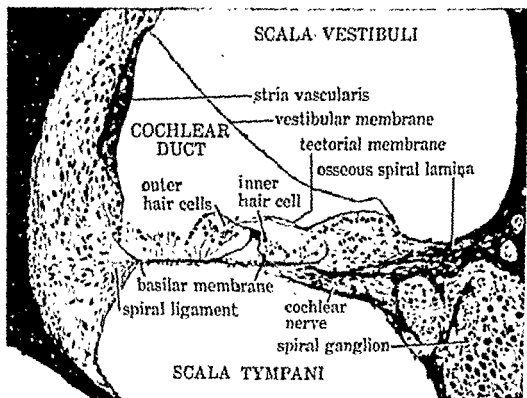
FIGURE 165. Cochlear duct with spiral organ (Corti); guinea pig. Photomicrograph, 125 ×.

epithelial cells, which stand upon the rather thick periosteum of the upper surface of the osseous spiral lamina. The structure of the spiral organ is portrayed in Fig 165. For detailed accounts of its structure, consult more advanced textbooks.

The hair cells of the spiral organ receive the terminal ramifications of the cochlear nerve fibers—fibers that arise as dendrons of bipolar neurons of the **spiral ganglion**. This ganglion lies in the **spiral canal** of the modiolus, as seen in Figs. 164 and 165.

The cochlear duct and osseous spiral lamina together subdivide the cochlea. Above and below them lie perilymph spaces that communicate with one another at the apex, where the cochlear duct ends blindly.

These perilymph spaces receive special names in the cochlea. That above the cochlear duct is the **scala vestibuli;** that below is the **scala tympani.** The scala vestibuli communicates freely with the perilymph spaces of the vestibule surrounding the sacculus. The scala tympani ends at the round window, which is covered by a thin membrane separating it from the middle ear. Both scalae are lined by a little connective tissue and a simple squamous epithelium like other perilymph spaces.

We shall leave the physiology of hearing to other courses. It is a fascinating subject but requires some speculation. Sound vibrations are transmitted to the fluids of the inner ear by the ossicles. They impinge upon the scala vestibuli through the oval window and set up force waves in the perilymph. How the hair cells are stimulated is not known. The harp-like basilar membrane may be caused to vibrate. Its lower short strings respond to higher frequencies of vibrations than its upper long strings. This appears to be part of the mechanism for selective sound analysis: high tones at the lower, and low tones at the higher end of the cochlear duct.

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   The organs of vision, hearing, equilibration, and smell are described in respect to development and adult structure. This is a clearly written account. Reading it will add considerably to your knowledge

2. Detwiler, S. R.: *Vertebrate Photoreceptors;* New York, The Macmillan Company, 1943
   Examine this short book (184 pages). It will provide details concerning the retina.

Integument

The integument or skin is far more than a protective hide to cover the body. It is an organ of great importance in regulating body temperature as well as in the reception of stimuli telling of changes in the external environment. It contains a substance that is a precursor of vitamin D. Other interesting functions are performed by the skin. Although its protective qualities are less well developed in man than in many other animals, it does very well without a heavy coat of hair. With adequate functioning of its blood vessels and accessory glands, it protects the body to a remarkable degree.

Cooling of the blood is accomplished readily because of the great vascularity of the integument and the efficient interaction of sweat glands, nerves, and blood vessels. Under resting conditions and moderate temperature surroundings, about 12.5 per cent of the heat produced in the body is lost through the skin. Almost 20 per cent of the daily fluid loss —450 cc. or more—is carried out through the skin. Under conditions of high external temperature and during exercise, more heat and greater quantities of water are dissipated through the integument. With this fluid go some of the body's precious electrolytes, notably sodium chloride.

The integument is an organ of considerable size, weighing between 3 and 5 kg. in the adult. It covers 0.25 sq. meters of surface at birth, increasing to 1.75 sq. meters at maturity. This sevenfold increase in surface area is accompanied by a twentyfold increase in body weight. Consequently, the ratio of skin area per kilogram of weight declines from 800 sq. cm. at birth to 300 sq. cm. in the adult.

The integument varies considerably in thickness and in structural appearance. It is thinnest on the eyelid and the tympanic membrane of the ear, measuring less than 0.5 mm. It is thickest on the back of the neck

and the palms and soles. On your own hands, it is probably 2 or 3 mm. thick, but it may reach 5 or 6 mm., or even more. on the palms of men who labor with their hands. Special structural features of the integument are hair, nails, and sebaceous and sweat glands.

SKIN

The skin is made up everywhere of two principal layers; the **epidermis,** which is epithelium, and the **corium,** which is connective tissue. The epi-
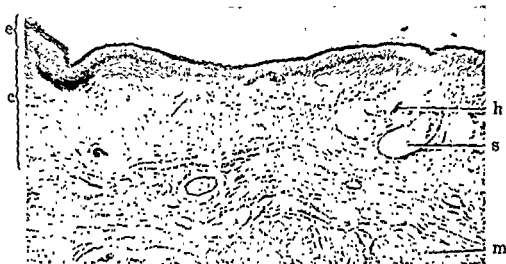
FIGURE 166. Thin skin of the human upper eyelid. This is one of the least highly developed types, consisting of narrow epidermis, *c*, and corium, *c*. The stratum corneum is a thin dark line on the surface. A sebaceous gland, *s*, and part of a hair follicle, *h*, are visible. The muscle of the eyelid, *m*, appears at the bottom on the right. Photomicrograph, 50 ×

dermis is completely avascular but does contain some nerve endings. The corium is richly supplied with blood and lymphatic vessels and has many kinds of nerve fibers and nerve endings in it. So richly supplied with nerve endings is the skin that some histologists describe it with the sense organs.

Corium. The corium is sometimes called the **derma.** It consists of an outer **papillary stratum** fitting closely against the epidermis and a coarser **reticular stratum** lying deeply. The outermost fibers of the papillary stratum are not only collagenous but also elastic and reticular. They are said to form a delicate basement membrane for the epithelial cells of the epidermis, but such a structure cannot be seen in ordinary preparations.

The reticular stratum of the corium blends with the subcutaneous con-

nective tissue, or *tela subcutanea,* called the superficial fascia in gross anatomy. It is usually quite impossible to say where the boundary lies (Figs. 166 to 168). Variable amounts of fat occupy the subcutaneous tissue. Among lobules of fat are found portions of the sweat glands, hair

FIGURE 167. Thin skin of a human wrist over the radial artery. This is thicker than that shown in Fig. 166 and has a wider epidermis, *e,* and corium, *c.* Two layers, stratum corneum, *co,* and stratum germinativum, *ge,* comprise the epidermis. Sweat glands, *sw,* in the corium show lighter secreting and darker duct portions. Subcutaneous tissue is indicated at *t.* Photomicrograph, 50 ×.

follicles, blood vessels, lymphatics, nerves, and nerve endings. Skeletal muscle occurs in a few places.

The division between corium and epidermis is very sharp, but it is not an even plane or a straight line in most places. The corium is thrown up into ridges and secondarily into papillae that project into *the epidermis* and alternate with similar downward projections from the epidermis. The connective-tissue **papillae of the corium** serve to increase the number of blood capillaries exposed to the basal epithelial surface of the epidermis. The papillae may be simple or complex. Most of them contain capillary

loops. Some have special nerve endings, such as the tactile corpuscles (Meissner), which are especially numerous in the papillae of the index finger.
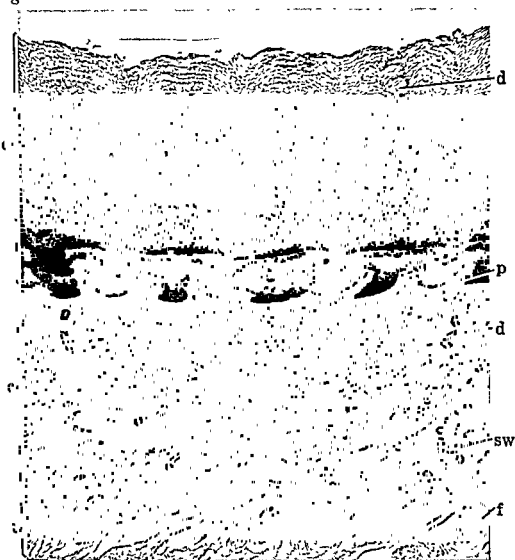
FIGURE 168. Thick skin from palmar surface of a human finger. This shows a heavy multilayered epidermis, *e*, the corium, *c*, and a small part of the subcutaneous tissue, *t*. Other abbreviations are *d*, duct of a sweat gland, *f*, fat, *p*, papilla of the corium; *sw*, sweat gland. Compare Figs. 166, 167, and 168. Photomicrograph, 50 ×.

Elastic fibers of the reticular stratum of the corium permit the overlying parts of the skin to move freely upon the more deeply placed tissues in most regions. Where they are few and where collagenous fibers predominate, the skin is less movable. The collagenous connective-tissue fibers of the corium are arranged roughly in layers tangential to the sur-

face of the skin. In many regions, there is a predominant orientation of
fibers parallel to one another. Consequently, puncture wounds of the skin
do not leave round holes but result in elliptical or slit openings, with the
long axis of the slit at right angles to the prevailing linear fibers of the
corium.

Epidermis of thin skin: The epidermis consists of stratified squamous
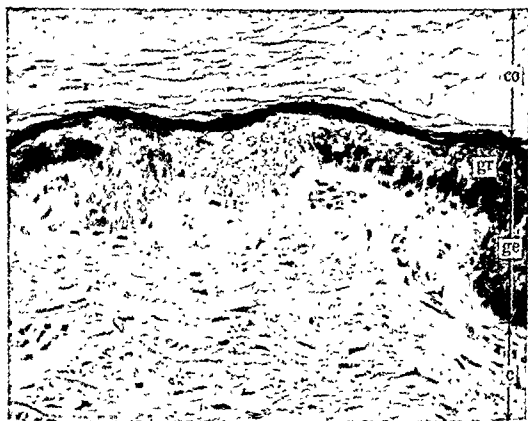
FIGURE 169. Skin of the wrist, showing stratum corneum, *co*, and stratum germi-
nativum, *ge*, clearly, and part of the corium, *c*. A single row of cells comprises the
stratum granulosum, *gr*. There is an imperfect stratum lucidum in the dark band.
Photomicrograph, 300 ×.

epithelium. It is divisible into two distinct strata in all regions and three
or four strata in many locations. Thin skin is the prevalent type. It usu-
ally presents only two clearly defined epidermal layers, as may be seen
in Figs. 166, 167, 169, and 170

The outer **stratum corneum** of the epidermis of thin skin is formed by
many layers of flat scale-like dead cells which stick together tenaciously
but are constantly being swept off the free surface They are replenished
by cells from the deeper, living strata.

The inner **stratum germinativum** is of variable thickness, greatest be-

tween the papillae of the corium. A basal row of columnar cells rests upon the connective tissue of the corium. Above this row of cells is a zone of polyhedral cells which usually appear to be covered with spines. These spines are delicate protoplasmic bridges connecting one cell with
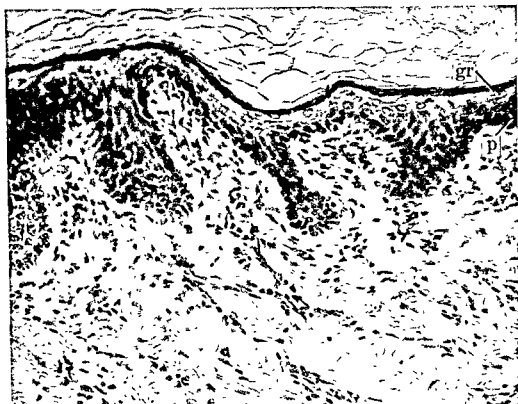
FIGURE 170. Genital skin of a Negro woman, with pigment in the basal cells, p, of the stratum germinativum. A narrow stratum granulosum, gr, is present. Photomicrograph, 300 ×.

another across the interstitial substance (Fig. 27). The outer cells of the stratum germinativum usually appear somewhat flattened.

In many regions, there is an abrupt transition to the stratum corneum, with little indication of the special layers characterizing epidermis of thick skin. Occasionally a single or double row of flat cells, whose cytoplasm contains dark granules, lies between the stratum germinativum and the stratum corneum. This constitutes a rudiment of the **stratum granulosum**. Sometimes an indefinite and incomplete **stratum lucidum** is found external to it. The skin of the wrist illustrates a type in which both these strata, thin but distinct, are usually present (Fig. 169).

Epidermis of thick skin. The epidermis of the hairless skin of the palms and soles differs from that of general body integument not only in thick-
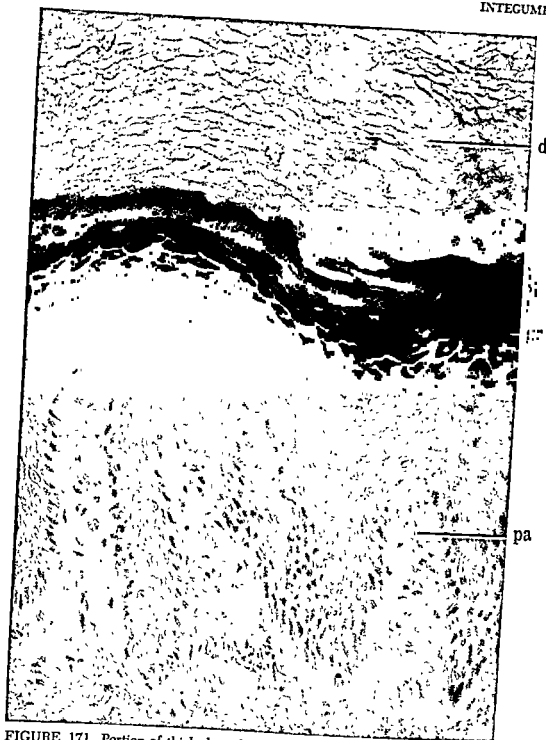
FIGURE 171. Portion of thick skin of a finger showing all layers of the epidermis. Designated structures are *d*, duct of a sweat gland; *gr*, stratum granulosum; *l*, stratum lucidum, *pa*, papilla of the corium containing blood vessels. Compare Figs. 169, 170, and 171. Photomicrograph, 300 ×.

ness but also in degree of specialization of its strata. The stratum ger-
minativum is thick and extensively indented by papillae of the corium.
Mitotic figures are frequently encountered, but they are by no means
confined to the basal layer. The greatest number of dividing cells occurs
in the middle third of the stratum germinativum

A stratum granulosum is formed by two to five rows of flattened cells
at the outer border of the stratum germinativum. Their cytoplasm con-
tains deeply staining granules which are precursors of the keratin found
in the dead cells of the outer cornified layer.

Just outside the stratum granulosum, a clear, highly refractive line ap-
pears in most sections. This is the stratum lucidum (Fig. 18B). It con-
tains a number of rows of flat cells containing **eleidin**, a substance formed
by dissolution of the granules from the stratum granulosum.

The stratum lucidum gives way abruptly to the stratum corneum. This
layer is very much thicker and firmer over the palms and soles than on
the general body skin. Compare the two types of epidermis in the accom-
panying photographs.

Skin color: Skin color is largely a function of the epidermis. The
stratum corneum has an inherent yellowish color due to its content of the
pigment, carotene. This is modified by blood color shining through from
the corium. All individuals except albinos possess melanin pigment.
Those of fair complexion have it confined to the cells of the deep layer of
the stratum germinativum (Fig. 170). In Negroes, it is found in all parts
of this stratum and may appear in the stratum granulosum as well. Mel-
anin is deficient in palmar and plantar skin and occurs in increased
amounts in genital, circumanal, and axillary skin, as well as in the areola
and nipple of the breast. The freckles of adolescence and senility are
small spots of increased melanin pigmentation. A physiological increase
in melanin production occurs after exposure to ultraviolet light or to the
summer sun of the bathing beach.

HAIR

The relative hairlessness of man is proverbial. It is more apparent than
real. Closer inspection will show that most of his body is covered with hair,
but it is fine, soft, and inconspicuous in many regions. Only a few places
lack hair. The palms and soles together with the dorsal aspect of terminal
parts of the digits are truly hairless. So are the red lip borders, the skin
of portions of both male and female genitalia, nipples of the mammary

FIGURE 172 Human scalp, compare with skin sections (Figs 166 to 168), but note that the magnification is less Designated structures are b, bulb of hair follicle, c, corium, e, epidermis, h, hair shaft; s, neck of a sebaceous gland, sw, sweat gland, t, subcutaneous tissue Photomicrograph, 30 ×.

glands, and the umbilicus Much of the body hair is the same in both sexes and is unaltered with sexual development and age. Puberty brings changes in hair, with which you are familiar. There are significant re-

FIGURE 173 Human scalp, showing bulbs of two hair follicles with indenting connective-tissue papillae Abbreviations are *con*, connective tissue continuous with the corium; *cu*, hair cuticle, *cs*, external root sheath, *f*, fat, *h*, hair, *is*, inner root sheath, *pa*, papillae Photomicrograph, 150 ×.

gional variations in its coarseness and length. Individual and racial varia-
tions are interesting, but their study properly belongs elsewhere.

Hair forms an important protective coat and heat insulator in most
mammals. It is impossible to make a good functional case for it in man,
except perhaps for hair of the scalp. The eyelashes serve a useful purpose.
The role of hairs in tactile perception seems worth while, although large
tactile vibrissae that characterize other mammals are missing in the hu-
man species. Human hair is not sufficiently important to give it much
space, and the student whose curiosity is unsatisfied by the present ac-
count is advised to turn elsewhere.

A hair consists of a **shaft** which is free and a root which is embedded
in a **hair follicle** (Figs. 172 and 173). The shaft is formed by cornified
cells whose outer single layer is called the cuticle. These cells are flat, like
the outermost flat cells of the stratum corneum of the skin. The inner cor-
nified hair-shaft cells are elongated. The cornified cells are formed from
living, actively dividing cells in the **bulb** of the hair follicle. They are
comparable with those of the stratum germinativum of the skin.

The hair follicle is an invagination of the skin into subcutaneous tissue.
All skin layers turn inward. The stratum corneum disappears down about
the level of the opening of sebaceous glands. The stratum granulosum, if
present, ends at about the same level. The stratum germinativum ends as
the **outer root sheath** of the hair, playing out at the base of the hair bulb.
The two layers of corium lie external to the outer root sheath with a base-
ment membrane between the papillary stratum and the root sheath itself.
The papillary stratum of the corium passes up into the hair bulb forming
a papilla, like those invaginating the stratum germinativum of the skin
(Fig. 173).

The **inner root sheath** of the hair extends up along the hair from the
bulb. It lies between the cuticle of the hair shaft and the outer root sheath.
It has a number of named layers which students never remember because
they are of no consequence. The inner root sheath plays out below the
openings of the sebaceous glands.

Smooth muscles of hair follicles, the **arrector pili,** attach to the fibrous
sheath of the hair follicle on the leeward side of the hairs. These muscles
extend diagonally past the sebaceous glands and insert into the papillary
layer of the corium. Contraction serves to elevate the hairs, also to de-
press the skin near the hairs to form goose flesh.

NAILS

Nails, like claws and hoofs, are a modification of the stratum corneum of the epidermis on the dorsal aspect of the terminal parts of the digits. They are horny plates overlying a well-developed stratum germinativum, called the **nail bed** (Fig. 174). A nail is rooted in a channel, the **nail**
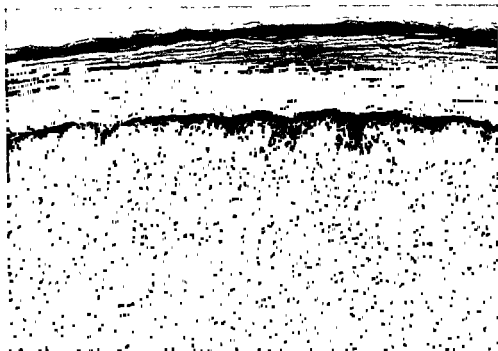
FIGURE 174. Fingernail sectioned transversely to show the ridges of the corium, compare with skin. Photomicrograph, 150 ×.

groove, which is formed by a flap of skin, the **nail fold.** Laterally, the nail borders upon the stratum corneum of the epidermis. The proximal nail fold carries the stratum corneum into the nail groove above the **root** of the nail. Stratum lucidum and stratum granulosum, when visible, end in the groove, and the stratum germinativum continues to meet that of the nail bed. The stratum germinativum is thickened and is called the **matrix** in the nail root, where active cell proliferation and nail growth occur. The corium of the nail bed has ridges arranged longitudinally, down which the nail glides from the matrix in the root as a launched ship glides down the ways (Fig. 174).

GLANDS OF THE INTEGUMENT

Glands associated with the skin and formed as ingrowths of it are the sebaceous, sudoriferous, apocrine, and mammary glands.

Sebaceous glands: These are holocrine glands of simple or, more rarely, branched alveolar types. Most **sebaceous glands** are associated with hair follicles, opening by means of short ducts lined with stratified epithelium continuous with that of the outer root sheath of the hair. They discharge their secretion, **sebum**, into the hair sheath at the neck of the hair follicle.

The secreting portion of the sebaceous gland is an ovoid mass of epithelial cells (Figs. 166 and 172). The outer rim is formed by a row of epithelial cells of the germinative layer resting upon a delicate basement membrane which is contributed by the corium. The inner cells, instead of being flattened, are greatly swollen with secretion droplets of a fatty nature. These cells are in an advanced stage of physiological degeneration (Fig. 18A). Their nuclei, when visible, are misshapen and pyknotic. When these cells disintegrate and discharge their secretion, replacements move up from more peripheral locations, especially from that portion of the rim nearest the gland neck.

Some very large and compound sebaceous glands are found in the skin of the nose and external ear, but their structure is no different from that of the more common variety. Special sebaceous glands, in the form of simple alveoli branching from a single duct, are found in the upper eyelid. These are the tarsal glands (Fig. 160). At the borders of hairless skin, sebaceous glands unassociated with hair follicles are found. The palms and soles lack sebaceous glands.

Sudoriferous glands: These are the **sweat glands.** They are simple, coiled tubules located in most areas of skin, absent only in the skin of the nipple, margins of the lips, concave surface of the external ear, and in portions of the genital skin. In some locations, they are very much less numerous than in other places. Few are found on the eyelid. There are about 90 per square centimeter on the leg, almost 400 per square centimeter on the palms and soles, and even greater numbers on the finger tips.

Most sweat glands are located in the reticular layer of the corium, although some of the larger ones are found in the subcutaneous connective tissue. They appear as tubes folded or coiled irregularly though rather tightly, and forming glomeruli embedded in fibrous connective tissue. Each glomerulus is about 0.1 to 0.5 mm. in diameter. The greater part of each glomerular coil is made up of the secreting portion of the tubule.

About one-fourth of the coiled portion is excretory duct. Sweat glands may be seen in Figs. 167 and 168.

The secretory part of the tubule is formed of simple columnar epithelium resting on a basement membrane which is contributed by the surrounding connective tissue of the corium. Between epithelium and basement membrane, some spindle-shaped myoepithelial cells are located (Fig 175). These contract and serve to hasten excretion of sweat under the influence of nervous stimulation.
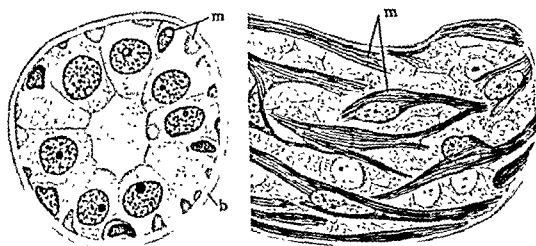
FIGURE 175 Secreting portions of a human sweat gland, showing myoepithelial cells, *m*, and basement membrane, *b* 600 ×.

Three parts of a **sweat-gland duct** can be distinguished. The first part is that which is folded among the secretory coils of the gland. It begins abruptly The myoepithelial cells end, and the columnar secreting cells give way to a double or triple layer of lower columnar cells which have darker cytoplasm than the secreting cells. The diameter of the duct is only about half that of the secretory duct. Sometimes a slight surface cornification of the cells next to the lumen can be observed. The second part of the duct runs toward the epidermis with which its cells blend (Fig. 168). The third part, especially where it traverses the thickened stratum corneum of the palms and soles, is twisted like a corkscrew (Fig. 176). As the duct enters the epidermis, its cells are lost among those of the stratum germinativum The basement membrane blends with the papillary stratum of the corium. The lumen is all that is left. It runs through the epithelium as an cleidin-lined twisted cleft.

The importance of the sweat glands can scarcely be overemphasized, although they are not indispensable for life. Occasionally they are defi-

cient or even largely absent. Their secretion is a watery fluid containing some solutes, mainly sodium chloride. A certain amount of moisture escapes directly from the skin, and evaporation of this imperceptible perspiration is sufficient to meet ordinary needs of the skin. The secretion of the sweat glands is essential in the regulation of body temperature during unusually warm weather and during exercise. Regulation of body temperature by the sweat glands, as in man, is a phenomenon that is not general among mammals.

FIGURE 176. Ducts of sweat glands traversing the stratum corneum of a human finger Carmine stain Specimen in the Piersol collection. Photomicrograph, 50 ×.

Apocrine glands of the skin: Special types of sweat glands are found in a number of places, differing from the ordinary sudoriferous glands, not only in size but also in mode of formation of secretion. They produce substances that are chemically different from sweat and contain portions of the cells that produce them (page 41). Apocrine glands occur in the skin of the axilla, scrotum, labia majora, and the circumanal regions. They develop or become enlarged at puberty, and those of the female undergo hypertrophy with each menstrual cycle. Structurally, the apocrine glands resemble ordinary sweat glands, but they measure from 1 to 5 mm. in diameter, are more deeply placed in the subcutaneous tissue, and empty into hair follicles instead of onto the surface of the skin. Myoepithelial cells are well developed in these glands.

Other somewhat similar apocrine glands are those of the areola of the breast, the ciliary glands of the eyelid margins, and the ceruminous glands of the external auditory meatus. The areolar glands are large compound tubular glands which may be considered transitional between

sweat and mammary glands. The ciliary glands of the eyelid are relatively straight, simple, or branched tubules. The ceruminous glands, larger than most others, have branched coiled secretory portions and often have branched duct systems. Their secretion is thick, filled with yellowish pigment, and solidifies upon exposure to the air, forming the ear wax.

Mammary gland: This is a very much hypertrophied gland of the integument. Because of its importance and its relation to endocrine function and the reproductive cycle, it is considered separately in the last chapter of this book.

VESSELS AND NERVES OF THE INTEGUMENT

The arteries that enter the skin from the subcutaneous connective tissues first form an anastomosing network, the cutaneous plexus in the reticular stratum of the corium. Small branches pass upward from this plexus into the papillary stratum, where another anastomosing network is located. This is the papillary plexus; it gives rise to the capillary tufts of the papillae of the corium as well as the little vessels that supply the sebaceous glands and upper portions of the hair follicles. The sweat glands and deeper parts of hair follicles are supplied by branches from the cutaneous plexus. Arteriovenous anastomoses are found in many locations, especially in the skin of the palms, finger tips, nail bed, and in the lips.

Venules collecting blood from capillaries of the papillae of the corium form a delicate papillary plexus. These flow into a network of larger venules between papillary and reticular strata of the corium. A third plexus is formed by the larger subcutaneous veins, and this receives tributaries from all parts of the skin.

Lymphatic capillaries are numerous in the papillary stratum. Collecting lymphatics are found more deeply, especially in the superficial fascia. They are not present in great numbers in deep fascia.

The integument is very well supplied with nerves and sensory nerve endings. All the nerve fibers are not in the sensory category. A great many enter the skin to supply the smooth muscle of blood vessels for the purpose of regulating the amount of blood flowing through this organ. Others end upon the smooth muscles of the hair follicles, the arrector pili, and the myoepithelial cells in the secretory tubules of the sweat glands.

The sensory nerve endings were described in Chap. 11. One of the main functions of the skin is the reception of stimuli from changes in the external environment. Not all regions of the skin are equally receptive. As you well know, the hands and feet, but especially the palmar surfaces of the fingers and that of the index finger in particular, are more richly supplied with tactile end organs than such regions as the thigh and back.

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Mouth and Pharynx

The process of digestion begins in the mouth. There food is mashed by the teeth and softened and lubricated by fluid and mucus secreted by many glands that open into the mouth. After chewing has moistened the dry food and reduced its coarseness, it is passed into the pharynx by the tongue. Swallowing is initiated in the oral pharynx, the vestibule of the esophagus. The mouth is more than a convenient starting point for a pleasant meal. Because of the roles it plays in speech and breathing and because the battle against invading microorganisms and toxins starts in the mouth, its lining membrane assumes considerable importance.

MUCOUS MEMBRANES

The entire digestive tract, like other passageways, is lined by a **mucous membrane**[1] whose characteristics vary in different parts. In its simplest form, a mucous membrane consists of epithelium resting upon a layer of connective tissue. The connective-tissue layer is called the **lamina propria** and is the stroma of the mucous membrane. It is often like the papillary stratum of the corium. It may be loose or fairly dense, and it contains a good many elastic fibers. In the lamina propria run many blood vessels, lymphatic vessels, and nerves, there may be some smooth muscle. Lymphatic tissue is commonly found in abundance in the lamina propria. A prominent **basement membrane** is often encountered just beneath the epithelium

The mucous membrane of the mouth and pharynx is fastened down to muscle, bone, or dense fibrous connective tissue in most places. In

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[1] The term mucous membrane does not imply that mucus is always secreted by it or even associated with it. The mucous membrane of the urinary bladder is an example of one that secretes no mucus

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some places, it is slightly attached to deep structures by a **tunica sub-mucosa** of looser connective tissue. Glands lie in the lamina propria or in the submucosa and empty by ducts onto the epithelial surface. Large glands, like the parotid, are found some distance away from the mucous membrane, upon which they pour their secretion. Part of the pharyngeal mucous membrane has goblet cells within the epithelium itself. These secrete mucus.

MOUTH CAVITY

The mouth cavity may be divided into vestibule, in front of the teeth and gums, and the mouth proper behind them. The tongue is in the mouth proper. The tonsils are located at the rear, where the mouth and oral pharynx join. The palate forms the roof.

The oral mucous membrane is a little like the skin. Its epithelium is stratified squamous, but it is thicker than that of most skin and is corni-fied in only a few places. The lamina propria projects into it to form connective-tissue papillae, like the papillae of the corium. These contain loops of capillaries, as well as nerve fibers ending in the epithelium.

Lips and cheeks: The **lips** and **cheeks** are formed principally by skele-tal muscles and fibrous connective tissue covered on the outside with thin skin and lined by the oral mucous membrane.

The **red margin** of the lips marks the transition between skin and mucous membrane. Its epithelium is thicker than that of the skin. The outer cells contain eleidin, for they are in the process of cornification. This renders them translucent and permits the richly vascularized lamina propria to be seen through them, imparting the red color to the lips. Hair and sweat glands stop abruptly at the margin, but a few sebaceous glands may be present beyond it. *Figure 177* shows the lip in low mag-nification.

The red margin blends at the inner lip surface with mucous membrane which has noncornified epithelium like that of the cheek. The lamina propria forms especially prominent papillae on the inner free margin of the red border. The mucous membrane of lips and cheeks blends with submucous connective tissue, dense strands of which serve to tie the mucous membrane down to underlying muscles and thus prevent it from getting in the way of the teeth during chewing.

Glands of the lips and cheeks are numerous. **Labial glands** form a ring about the oral opening at the inner border of the red margin. They are

principally tubulo-acinous mucous glands, although a few groups of serous cells are present. Glands of the cheeks are called **buccal glands** in the submucosa and **molar glands** outside the muscle of the cheek near the parotid duct. Both are predominantly mucous glands.
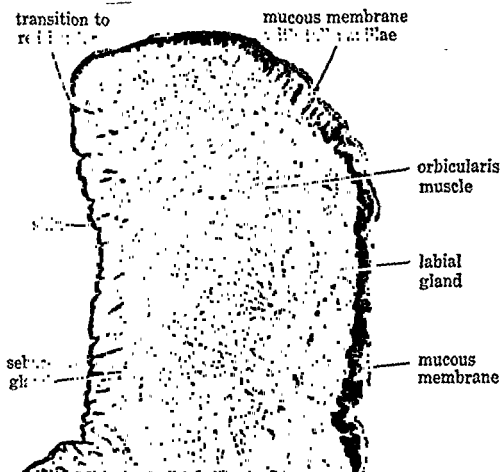
FIGURE 177. Human lip, showing the transition from skin to mucous membrane. The red lip border has prominent connective-tissue papillae Specimen in the Piersol collection (see Piersol's *Normal Histology*, 14th ed, Fig 177, Lippincott, 1929). Photomicrograph, 15 ×.

Gums or gingivae. **Gums** are formed by mucous membranes reflected onto the alveolar portions of the mandible and maxilla from the lips, cheeks, floor of the mouth, and palate. The basal cell layer of the gingival epithelium may be pigmented in dark-skinned individuals, especially in Negroes. The superficial squamous cells are often cornified, and a stratum granulosum may be present. Cornification is related to abrasion by coarse food. The epithelium turns down at the margin along the teeth, lining one side of a potential cleft, the other side of which is

formed by tooth enamel in youth and cementum in the aged (Fig. 178). The lamina propria of the gums is dense and firmly anchored to sub-
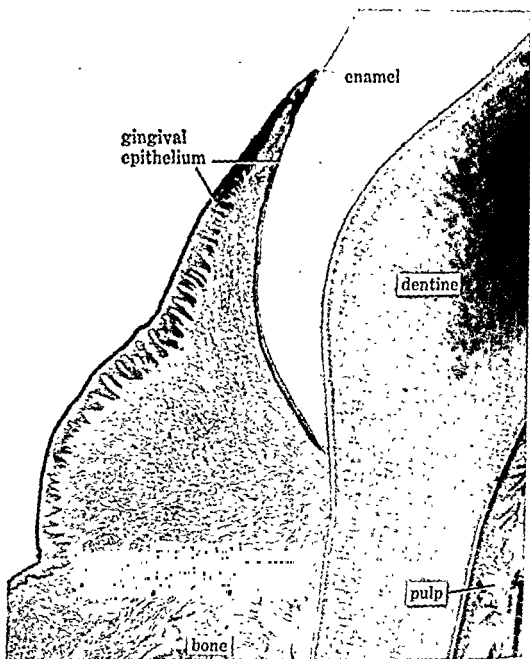
FIGURE 178. Junction of gum and tooth Decalcified preparation in which the enamel has been dissolved leaving a clear space Photomicrograph, 40 ×.

jacent periosteum. Its connective-tissue papillae are very tall. No glands are present in the gums.

Palate: The roof of the mouth is formed by the palate. The mucous membrane of the gums of the upper jaw is continuous with that covering

FIGURE 179. Soft palate, showing the oral surface below and the nasal surface above Photomicrograph, 40 ×.

the **hard palate.** This membrane is firmly united with subjacent perios-teum. Its epithelium resembles that of the gums and has cornified cells on its surface. Numerous **palatine glands,** composed of mucous acini

with small ducts, are found beneath the mucous membrane. Irregular transverse ridges characterize the anterior part of the hard palate.

The **soft palate** is formed of mucous membranes on two sides of a layer composed of skeletal muscle, fibrous connective tissue, and glands, as seen in Fig. 179. At the place where the mucous membrane folds over the free surface, a prolongation of the palate hangs down into the mouth. This is the **uvula**. The oral side of the soft palate and uvula are covered with noncornified stratified squamous epithelium. The pharyngeal side resembles the oral side for a little way beyond the border, but then becomes lined with pseudostratified epithelium with cilia and goblet cells. The lamina propria lacks the high connective-tissue papillae seen in some other places. It is connected with the layer of mucous glands by many elastic fibers. Lymphocytic infiltration is usually encountered in the lamina propria and epithelium.

TONGUE

The **tongue** is an organ of no mean importance. Not only is it a device for making speech possible and the tool for moving food, but it is the great tester of substances that enter the mouth, accepting or rejecting the materials to be submitted to the digestive organs. It is an important sense organ, richly endowed with nerve endings for touch as well as special endings for taste and chemical sense. The tongue may be thought of as an evagination of the mucous membrane of the mouth floor by a mass of skeletal muscle.

Mucosa and submucosa: The mucous membrane of the tongue is closely adherent to the subjacent muscle. A submucosa is present only on part of its lower surface. The mucosa on the underside is thin and loose. This is especially true at the **frenulum** of the tongue, where it joins the mucosa of the floor of the mouth.

The mucous membrane of the undersurface is quite smooth. That of the borders and anterior two-thirds of the upper surface is peculiarly roughened by many fine projections (Fig. 180). These are the tiny **lingual papillae** that give this **papillary area** a plush-like appearance. The posterior one-third of the dorsal surface has an irregularly bumpy appearance and lacks the fine plush of the anterior two-thirds. It is characterized by lymphatic nodules in the lamina propria and is called the **lymphatic area**. The boundary between these two portions of the mu-

cosa is marked by a V-shaped sulcus in the infant. This sulcus disappears and the row of vallate papillae lies near the boundary in the adult.

Lingual papillae: The papillary area of the lingual mucous membrane is beset by the lingual papillae, some of which are illustrated in Fig. 180.

FIGURE 180 Human tongue, showing the junction of the rough papillary dorsal surface with the smooth lateral surface. Note the interlacing muscle bundles running in three planes. Photomicrograph, 7 ×.

Most numerous are **conical** and thread-like **filiform papillae.** Many have brushes of secondary papillae on their tops. The papillae tend to occur in multiple rows, parallel to the V-shaped sulcus and radiating outward and forward from the mid-line of the tongue. The taller conical papillae may project as much as 3 mm. The surface epithelial cells are flattened, although they are not cornified in man. The lamina propria ex-

tends into the base of each papilla a little way but not far enough to give the papilla a pink color.

Fungiform papillae are small mushroom-shaped projections scattered over the tongue surface in small numbers. They are visible as little red spots, because the lamina propria comes close to the upper surface where the epithelium is thin. These papillae are lower and thicker than the conical papillae. Some have taste buds.

The **vallate papillae** are the largest (Fig. 181). There are seven to
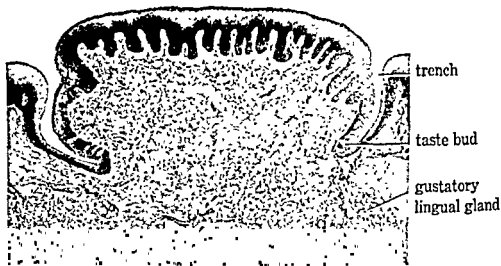
FIGURE 181. Vallate papilla, human tongue. Photomicrograph, 40 ×.

eleven of these arranged in a V-shaped line at the rear of the papillary area. They do not rise above the level of the other lingual papillae, but each is surrounded by a moat, 1 to 1.5 mm. deep. They measure 1 to 2 mm. across the free surface. A ring-shaped wall of mucous membrane, nearly free of filiform projections, encircles each vallate papilla. Taste buds are always numerous in the epithelium lining the moat. Ducts of the serous gustatory lingual glands empty into the bottom of the moat, keeping it full of clear fluid which serves as a solvent for particles of food substances to be tasted.

Foliate papillae may be found at the side of the tongue, just in front of the anterior palatine arch. They are rudimentary in man but well developed in some animals. When present, they appear as parallel vertical folds of the mucosa.

Taste buds: These are small ovoid bodies embedded in the stratified squamous epithelium of the tongue. Each **taste bud** occupies an entire thickness of epithelium from lamina propria to a little opening, the **pore canal**, on its free surface. Taste buds are widely scattered but are most

numerous studding the walls of the moat surrounding each vallate papilla. They are not confined to the tongue, having been found in the palate, pharynx, and even the epiglottis. Their number is greatest at birth. Taste buds in a trench between foliate papillae of a rabbit are shown in Fig. 182.

FIGURE 182. Taste buds lining a trench between foliate papillae of a rabbit, one (marked, *p*) shows a pore canal. Photomicrograph, 300 ×.

Each taste bud is formed by a number of tall columnar epithelial cells bunched together something like segments of an orange. An occasional low basal cell may be seen. Among the tall supportive cells is a smaller number of thin elongated neuroepithelial **gustatory cells**, usually two to five. At the outer pole, each neuroepithelial cell ends in a short hair-like process which lies in the pore canal of the taste bud. Special sensory nerve fibers enter the taste bud from the lamina propria and end around and upon the gustatory cells.

Lingual tonsils: The lymphatic area of the lingual mucous membrane is coarsely roughened by the subjacent lymphatic nodules. These are arranged around tubular depressions or crypts of the surface epithelium. The lymphatic nodules and their epithelial crypts form the **lingual tonsils**. These resemble the palatine tonsils but are simpler and are not encapsulated with connective tissue. Their epithelium is heavily invaded by lymphocytes from the underlying lymphatic tissue of the lamina propria.

Lingual muscles: The skeletal muscles of the tongue are both extrinsic and intrinsic. The intrinsic muscles form its bulk. A layer of dense fibrous connective tissue forms the **lingual septum** which divides the tongue longitudinally into two halves. The intrinsic muscles are arranged in longitudinal, vertical, and transverse planes. A transverse section through the tongue will show muscle fibers cut across and others parallel to the cut surface. The interlacing of muscles is illustrated in Fig. 180.

Much fibrous connective tissue separates muscle bundles and conducts blood vessels, lymphatics, and nerves through the substance of the tongue. Connective tissue is loose at the root of the tongue, permitting it to move freely. Fibers of the intrinsic muscles attach to the connective-tissue septum and to the lamina propria of the mucous membrane. Branching fibers occur in this location.

Lingual glands: There are three groups of glands embedded in the connective tissue among muscle bundles. All are small tubulo-acinous glands with numerous small ducts.

The **anterior lingual glands** occur in groups, measuring about 8 by 16 mm. They lie on either side of the frenulum beneath the tip of the tongue. Their mixed mucous and serous acini extend deeply in among muscle bundles and open by about five ducts on either side of the oral cavity.

The **posterior lingual glands** are mucous. They occur just in front of the most medial vallate papilla, along the margins of the tongue near its root, and under the mucosa of the lymphatic area. Ducts are numerous. Some empty into the crypts of the lingual tonsils.

The **gustatory lingual glands** (Ebner) have been mentioned. They are purely serous and lie deeply among muscle bundles in the vicinity of the vallate papillae. Their ducts open into the moats surrounding the papillae.

TEETH

Teeth are the most unusual products of living cells, being formed in part by a flint-like material, the hardest substance in the body. Teeth are actually elaborate dermal papillae, as will be readily appreciated in considering their development.

The **crown,** or projecting portion of each tooth, is capped with **enamel,** the product of ectodermal cells. The main body of the tooth, including its **roots** extending below the level of the gums, is of mesodermal origin and is composed of ivory-like **dentine.** Encasing the dentine below the **neck** of the tooth at the gingival border, is a thin layer of bone-like **cementum.**

Outside the root and anchoring the tooth in its socket in the alveolar processes of the jaws is dense fibrous connective tissue, forming the **peridental membrane.** The center of the dentine has a hollow **pulp cavity** in the dry tooth, but in life this is filled with a loose type of connective tissue, the **pulp.** At the tip of each root, the pulp merges with the connective tissue of the peridental membrane through a minute **apical foramen.** Wherever there is connective tissue, there are blood vessels and nerves, and these make the peridental membrane and pulp vital parts of a tooth.

Pulp: The tooth pulp contains delicate reticular and collagenous fibers. Its stellate cells resemble mesenchyme. Interstitial matrix substance is mucoid and contains much tissue fluid. Pulp may be seen in Figs. 178 and 186

Pulp cells adjoining the dentine are modified so that they resemble simple columnar epithelium They are the **odontoblasts.** They are somewhat like osteoblasts but never get caught in developing matrix, as do bone cells. Processes of the odontoblasts extend into the pulp. One or two thin processes also pass into the dentine as the **dentinal fibers.** Odontoblasts take part in dentine formation during tooth development In later life, irritation of dentine may lead to renewal of this activity in building secondary dentine.

The pulp has a rich capillary plexus arising from arterioles that enter the apical root canals. Nerve fibers for the arterial smooth muscle are unmyelinated. Those for sensory innervation of the pulp are small myelinated fibers. Free nerve endings occur about the odontoblasts, but few pass into the dentine and none goes far The extreme sensitivity of dentine to pain may indicate that the odontoblasts, with their long dentinal fibers, serve as receptor cells.
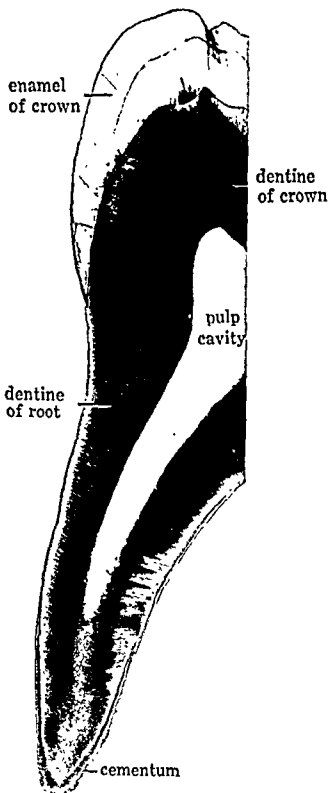
FIGURE 183 Human molar tooth: part of a
ground and polished dry section Photomicrograph,
8 ×.

Dentine: This lacks cells and is nonvascular, but its organic materials are constantly exchanged like those of bone. It is harder than bone, which it resembles slightly. It has a fibrillar background impregnated with calcium salts. Dentine may be seen in Figs. 183, 184, and 186.

FIGURE 184. Dentine-enamel junction of a human tooth, a ground and polished dry section. Note the parallel dentinal tubules extending upward toward the enamel, the light upper half, and their terminal branching. Photomicrograph, 150 ×.

Dentinal canaliculi contain the processes of the odontoblasts. These canaliculi measure 2 to 5 μ in diameter, diminishing as they extend through the dentine toward the enamel or cementum. Fine anastomosing branches are given off by them. The main canaliculi pursue parallel courses (Fig. 184).

An outer layer of dentine, especially prominent in the root of the tooth, lacks parallel canaliculi but has many very small spaces and fine canaliculi that run in all directions. This is called the **granular layer** (Tomes).
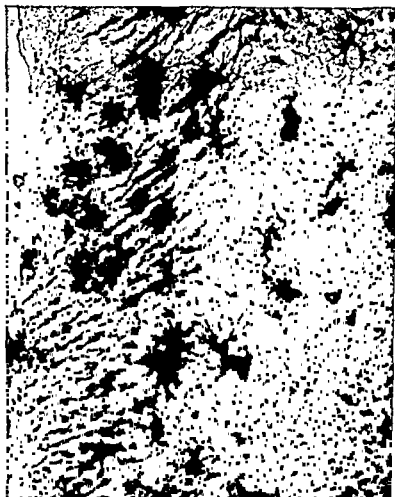
FIGURE 185. Cementum with lacunae of stellate cementum cells; a ground and polished dry section. The dentine is toward the right, the peridental membrane is toward the left Photomicrograph, 300 ×.

Enamel: Hard as flint, enamel contains less than 4 per cent organic material. Consequently, practically nothing is left when it is decalcified with acid. It is built up of parallel rods, called **enamel prisms.** Each of these is secreted during development of the tooth by one epithelial cell of the enamel organ The enamel prisms are separated from one another by a minute amount of organic substance. Enamel lasts a lifetime, wearing away somewhat in old age but outlasting other products of living cells.

Cementum: Of all the tooth components, cementum most closely resembles bone. It has **lacunae** and **cementum cells** whose processes radiate out into canaliculi. Haversian systems are usually absent. The cementum presents a more suitable attaching surface than dentine for fibrous connective tissue. It is shown in Fig. 185.

Peridental membrane: This membrane is an inelastic, dense, fibrous connective-tissue layer around each tooth root. It serves also as periosteum for the alveolar processes of the jawbones. Furthermore, it anchors one tooth to another and cushions the teeth in their sockets. From its cells are derived osteoblasts on the one side and analogous **cementoblasts** on the other. Osteoclasts are present during resorption of deciduous teeth. When they occur *in relation to the cementum and dentine,* they are sometimes called **odontoclasts.**

A vitalizing plexus of blood vessels courses through the peridental membrane. Myelinated nerve fibers are larger than those in the tooth pulp. They transmit messages of pressure and touch.

DEVELOPMENT OF TEETH

All teeth begin to form beneath the epithelium of the gums in prenatal life, but none pierces the epithelium to erupt into the mouth cavity until about six months after birth. For twenty years, or even longer, growth changes and the accompanying series of eruptions of teeth take place in the jaws. Therefore, the formation of teeth, like the formation of bones, belongs in the realm of normal histology as well as embryology.

Two sets of teeth are formed. The child is provided with **deciduous** or milk teeth during the first two years. These teeth are replaced by permanent teeth, beginning about the sixth year. The growth processes are similar in both dentitions.

The first evidence of tooth formation is found in the embryo of 20 mm. length and consists of a thickening of the ectoderm in a curved dental lamina. This occurs in each jaw, just inside the primordium of the lip furrow. Buds of epithelial cells from this lamina invaginate the subjacent mesenchyme to form **enamel organs** for the deciduous teeth These are cup-shaped and enclose a mass of mesenchymal cells, the **dental papilla,** which is the primordium of the pulp and gives rise to the dentine. Soon, each enamel organ exhibits outer and inner layers of epithelial cells, with the cells in between becoming stellate, resembling reticular connective tissue and forming the **enamel pulp.** The inner epithelial cells are impor-

tant ones. They become tall columnar and are called **ameloblasts** when they begin to secrete the enamel precursor substance. The cells of the adjacent pulp mesenchyme heighten to become **odontoblasts** which en-
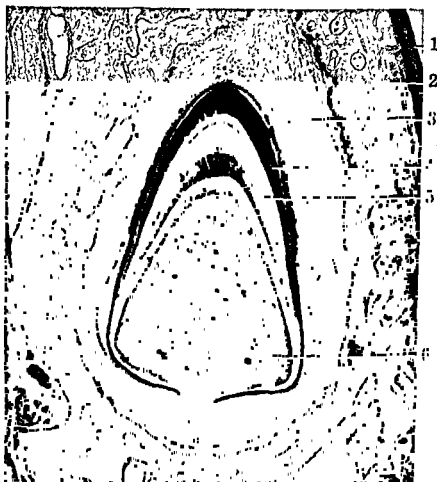
FIGURE 186A. Developing tooth: an uncrupted tooth in its alveolar space showing the following: 1, gum, 2, bone, 3, connective tissue, 4, enamel, 5, dentine; 6, pulp. Photomicrograph, by Nonidez, approximately 20 ×.

gage in the process of dentine formation. The two processes go on simultaneously. Meanwhile, the jawbones grow apace.

Enamel deposition begins at the end of the fourth month of prenatal life in the deciduous teeth. As a tooth develops, the enamel organ becomes confined to the part that will be the crown. With completion of enamel formation, the ameloblasts disappear. They leave a thin trace, the **dental cuticle**, on the enamel surface of the erupting tooth.

The odontoblasts persist but ordinarily build no more dentine after tooth development and eruption are completed. Roots are not fully

formed until just before eruption. They are attached to the growing jaw-
bones by a loose follicular sheath of embryonal connective tissue which
later forms the peridental membrane and the cementum of the root.

FIGURE 186B Developing tooth: a small portion of a similar tooth
showing the following layers from above downward. 1, enamel pulp; 2,
ameloblasts; 3, enamel; 4, calcified dentine, 5, noncalcified dentine, 6,
odontoblasts; 7, tooth pulp Photomicrograph, 150 ×

The deciduous teeth arise in five forward buds of the dental lamina of
the embryo Later on, other buds behind these give rise to the permanent
molar teeth which have no deciduous precursors. Furthermore, a second-
ary bud appears on the lingual side of each deciduous tooth germ. This
forms the enamel organ of the replacing permanent tooth, which is only
partly calcified before birth

GLANDS OF THE ORAL CAVITY

Numerous glands take part in production of saliva. Most of them are small and lack extensive duct systems. They are branched tubular and tubulo-acinous in type with mucous, serous, or mixed secreting portions. The small salivary glands have been described in connection with the lips, cheeks, palate, and tongue. Three large glands yet to be considered are the **parotid, submandibular** (submaxillary), and **sublingual.**

Each gland consists of secreting acini, tubules, and duct systems, all of which constitute the parenchyma of the organ, and a supporting framework of fibrous connective tissue, the stroma. A definite fibrous connective-tissue capsule is present in the parotid and submandibular glands but is lacking in the sublingual gland. Septa of connective tissue subdivide the parenchyma into lobes and lobules. Blood vessels, nerves, and the major subdivisions of the ducts traverse these septa.

Duct systems: Each gland is composed of a branching system of ducts which serve to carry away the secretion and pour it into the mouth cavity. These are called **excretory ducts.** The main excretory duct, in each instance, is lined with stratified squamous epithelium at the point of its opening into the mouth. Elsewhere it is formed by a two-layer stratified columnar epithelium or a pseudostratified epithelium. As they break up into smaller subdivisions, these ducts become lined with simple columnar epithelium (Fig. 187C). The excretory ducts have dense fibrous connective-tissue walls, and the largest, notably the main duct of the submandibular gland, may contain a few smooth-muscle cells. The smaller subdivisions of the excretory ducts enter the lobules of the glands and are divided further into secretory ducts.

The **secretory ducts** are formed of simple columnar epithelium, the cells of which are striated. This may be indicative of some secretory activity in their cells. In the parotid and submandibular glands, the secretory ducts branch into much smaller **intercalated ducts,** made up of flattened or low columnar epithelial cells. These, in turn, open into the secreting tubules or acini. Figures 187A and B show secretory and intercalated ducts.

The secreting acini of the salivary glands are formed of pyramidal columnar cells resting upon a basement membrane. Between the columnar cells and the basement membrane are found a few stellate cells resembling the myoepithelial cells of the sweat glands (Fig. 188). The se-
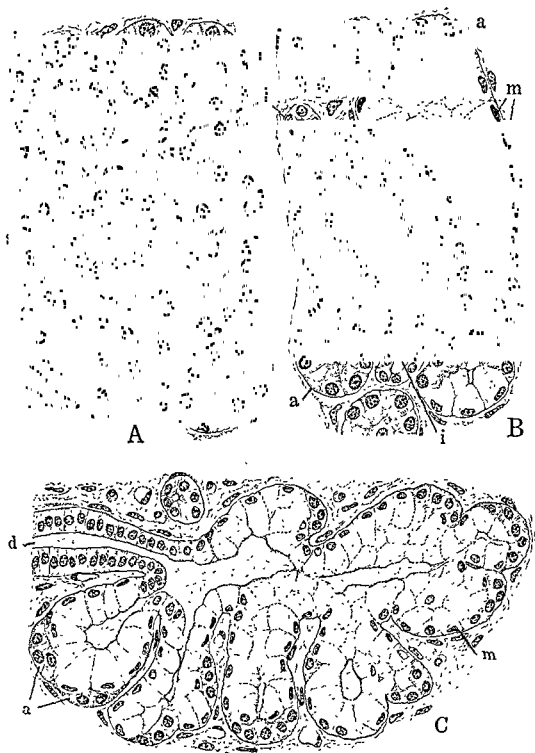
FIGURE 187 Human salivary glands, *A*, parotid, *B*, submandibular, *C*, sublingual:
a, serous acini and serous cells; *m*, mucous cells; *i*, intercalated duct, *s*, secretory
duct, *d*, excretory duct. 600 ×

creting cells are of two types, serous and mucous, both of which have been described previously (page 45) and are illustrated in Fig. 187.

Parotid gland: The only purely serous glands in the mouth are the gustatory lingual glands (Fig. 181) and the parotid glands (Fig. 189). The parotid, the largest of the salivary glands, is located in front of the ear in relation to the ramus of the mandible. It possesses a single large duct which opens into the vestibule of the mouth opposite the upper second molar tooth.
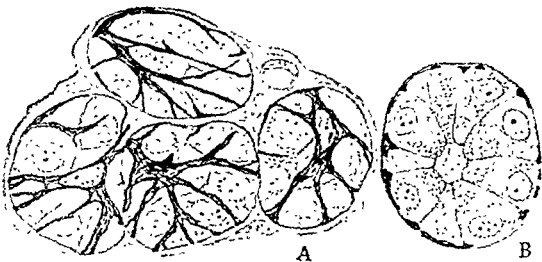
FIGURE 188. Branching myoepithelial cells of serous acini, salivary gland of a pig: A, surface view; B, sectional view. 600 ×.

The secreting tubules and acini are elongated and branching. They empty their secretion into the narrow intercalated ducts. These are numerous and relatively long in the parotid gland. The intercalated ducts enter secretory ducts which are lined with simple columnar epithelium.

The fibrous connective-tissue septa of the parotid gland contain a good deal of fat, which imparts a characteristic appearance to this organ. The amount of fat increases with age. Figure 189 illustrates this organ.

Submandibular gland: This is very largely a serous gland in man, although not in all species of animals. In the human gland, mucous acini are few.

The submandibular gland is located beneath the mandible in the floor of the mouth. It empties its secretion through a single main duct, opening into the mouth cavity on either side of the frenulum of the tongue. The excretory duct and its branches are similar in structure to those of the parotid gland.

The secretory ducts of the submandibular gland are more numerous

and longer than those of the parotid. On the other hand, the intercalated ducts are short and difficult to observe. Mucus-secreting tubules and acini, when present, are distinct from the predominating serous variety.

FIGURE 189 Human parotid gland; note the fat cells among serous acini. Photomicrograph, 150 ×.

Some of them are capped with serous cells, which appear in sections as semilunar groups, the demilunes. These groups of serous cells open into the same lumen with the mucous cells. Figure 190 shows the human submandibular gland.

Sublingual gland: The sublingual gland is a mixed gland in the forward part of the mouth just beneath the mucous membrane. Its structure varies

from lobe to lobe. As a matter of fact, it is actually made up of a grou of glands with several separate ducts pouring their secretions into th anterior part of the mouth cavity beneath the tongue.

FIGURE 190. Human submandibular gland, predominantly serous. Note one large duct in the stroma at the upper left and many small intralobular ducts. Specimen from Prof. L. B. Arey Photomicrograph, 150 ×.

Mucous tubules and acini predominate in the sublingual gland. Most serous cells occur in demilunes upon the mucous acini. Few, if any, inter-calated ducts will be found in the sublingual gland. The secretory ducts become directly continuous with the tubules and acini. The duct system of the sublingual gland is the least prominent of all the major salivary glands. Figure 191 shows the human sublingual gland.

ORAL PHARYNX

The mouth opens into the oral pharynx at the palatine arches, which are folds of mucous membrane formed at the sides of the free posterior
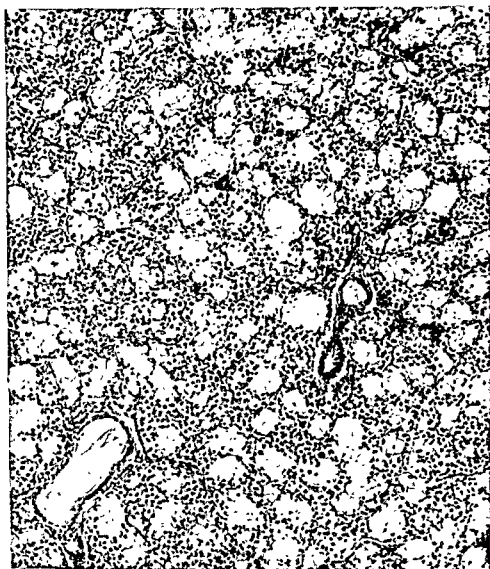
FIGURE 191 Human sublingual gland. Note the predominance of mucous acini; ducts are few and contain mucus. Specimen from Prof. L. B. Arey. Photomicrograph, 150 ×.

borders of the soft palate. The oral pharynx joins the nasal pharynx above and the laryngeal pharynx below. It plays an important part in the act of swallowing.

The **pharynx** is the throat. It is a musculofibrous sac, lined by a

mucous membrane similar to that of the mouth. Its wall has an outer muscular layer formed by the pharyngeal constrictors and associated muscles, all of the skeletal variety. Dense fibrous connective tissue con-
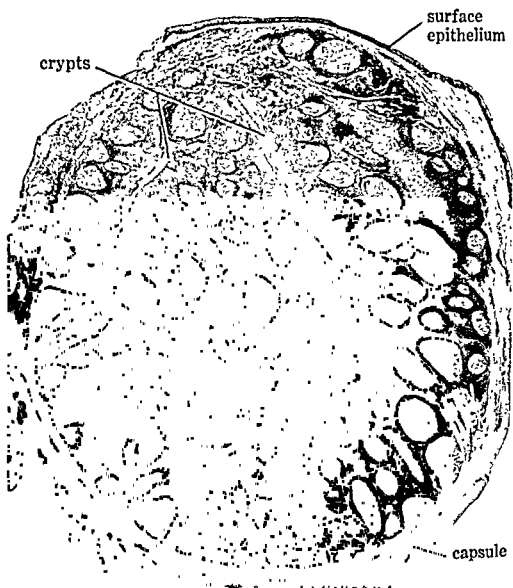
FIGURE 192. Human palatine tonsil. The mucous membrane has been torn away on the left. Photomicrograph, 8 ×.

taining many elastic fibers forms a submucous layer between muscularis and mucosa.

The mucous membrane consists of epithelium and lamina propria. The epithelium is stratified squamous, becoming continuous above in the nasal pharynx with the pseudostratified variety. The lamina propria is formed of reticular and loose fibrous connective tissue. An abundance of lym-
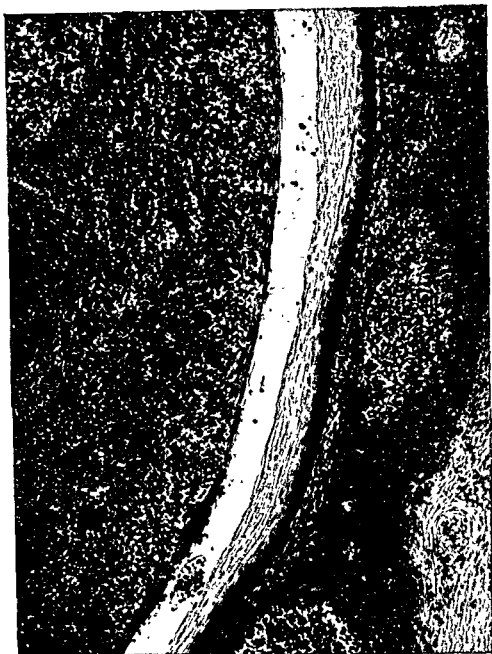
FIGURE 193 Crypt of the palatine tonsil. The epithelium of the right wall is intact, while that of the left wall is very largely replaced by invading lymphocytes Photomicrograph, 150 ×.

phatic tissue characterizes the mucous membrane of the pharynx. This lymphatic tissue is diffuse in some places and compact in others, with many lymphatic nodules occurring in aggregates.

Tonsils. The aggregates of lymphatic nodules of the pharynx form especially large masses, encapsulated or partly so, which are called tonsils.

In the lateral pharyngeal wall they form the **palatine tonsils**. Similar accumulations of lymphatic nodules are found in the posterior wall of the nasal pharynx, around the opening of the auditory tubes, and at the root of the tongue. These are the **pharyngeal, tubal,** and **lingual tonsils**.

The palatine tonsils are compound aggregates of lymphatic nodules, about 20 mm. long and 15 mm. wide, encapsulated in dense fibrous connective tissue which is continuous with the pharyngeal submucosa. The tonsilar surface is covered with stratified squamous epithelium. This is invaginated into the subjacent lymphatic tissue to form pits of varying depth. These are the **tonsilar crypts**. Each crypt may branch into a number of subdivisions. Figure 193 shows a crypt in the human palatine tonsil.

Little fibrous tissue will be seen in the lamina propria because of the abundance of lymphocytes. Lymphatic nodules with germinal centers abound beneath the tonsilar epithelium. Invasion of the epithelium by lymphocytes and escape of lymphocytes into the crypts are prominent features of the tonsils. Desquamated epithelial cells, lymphocytes, bacteria, and detritus will be seen in the crypts of even the healthiest tonsils.

Tonsils lack afferent lymphatic vessels, but they have efferent vessels which convey great numbers of lymphocytes to the blood stream (Fig. 105A). The function of the tonsils is lymphocyte production. They are organs of major surgical importance; they can be removed so easily, with little harm to the patient and much benefit to the surgeon.

The pharyngeal tonsil is similar in structure to the palatine tonsil. It is located on the posterior wall of the nasal pharynx and is covered with pseudostratified epithelium. Enlargement of the pharyngeal tonsil forms the adenoids, especially prominent during childhood.

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   Consult this book for good photographs Read portions here and there.
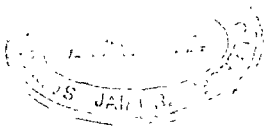
Tubular Digestive Organs

The digestive organs receive a great variety of substances from the external environment, which they help remake into the tissues of your body. The processes involved in this rebuilding are numerous and varied. They include mechanical and chemical disintegration of food, solution in digestive secretions, absorption of dissolved and altered usable materials, and excretion of the unusable residue.

GENERAL STRUCTURAL PLAN

From the pharynx to the anal canal, the digestive tube consists of various arrangements of four principal layers, called tunics: the mucosa, the submucosa, the muscularis, and the adventitia or serosa. The accompanying low-power photomicrograph of a section through the esophagus illustrates, rather diagrammatically, this general structural plan (Fig. 194).

The **tunica mucosae** of the digestive tract, like that of the mouth and pharynx, is innermost. It is the mucous membrane. It has three components: the epithelium, lamina propria, and muscularis mucosae. Below the esophagus, the epithelium is beset with innumerable pits and glands. In some places, where absorption takes place, the epithelium and lamina propria are thrown up into folds and into finger-like villi, which protrude into the lumen. Variations in the structure and arrangement of the epithelium characterize different portions of the digestive tube.

The lamina propria underlies the epithelium, enters into formation of its basement membrane, and fills the space between pits and glands. It consists of areolar and reticular tissue, filled with lymphocytes, which transform it into loose, or compact, lymphatic tissue in many places. Lymphatic nodules, single and aggregates, and many small glands occur

in it. Throughout this layer course lymphatic vessels, blood vessels, and nerves.

The muscularis mucosae is a thin layer or two of smooth muscle, marking the outer boundary of the tunica mucosae.
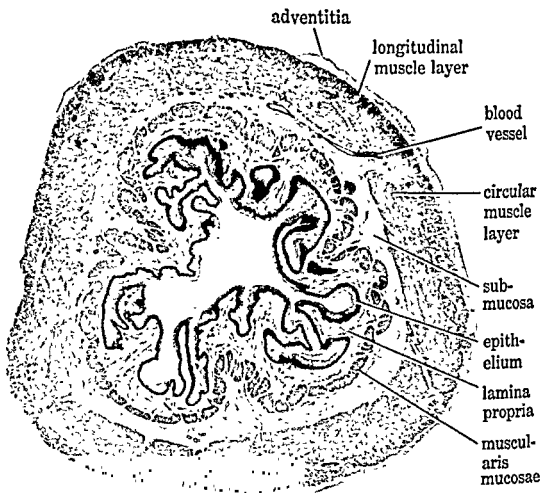
FIGURE 194. Human esophagus, illustrating the general plan of the tubular digestive organs. The section is from the upper one-third of the esophagus, the outer layer of muscle is mainly skeletal. Photomicrograph, 12 ×.

The **tunica submucosae** is the fibrous connective tissue beneath the mucous membrane. Through it course larger vessels as well as plexuses of autonomic nerve fibers containing groups of nerve cells.

The **tunica muscularis** consists of two principal layers. Throughout most of the digestive tract, these are composed of smooth muscle. The inner layer is circular. The outer is longitudinal, thickest in the esophagus and thinnest in the colon where it is reduced to three longitudinal bands. The circular muscle is thickened in several places to form sphincters. A

small amount of fibrous connective tissue, containing blood vessels and nerves, permeates the bundles of smooth muscle. A ganglionated autonomic nerve plexus is found between the circular and the longitudinal layers.

The **tunica adventitia** is the outermost coat of the digestive tube. It is formed of fibrous connective tissue blending with that of the surrounding structures in the esophagus and rectum. The portions of the digestive tract lying in the abdominal cavity have a layer of mesothelium over the surface of the adventitia. This transforms the tunica adventitia into a **serosa,** which is the visceral peritoneum (page 213).

ESOPHAGUS

The esophagus is insignificant in digestive processes, for it is nothing more than a short tube connecting the pharynx with the stomach and conveying the food bolus and fluids to the latter receptacle. Mucous glands lubricate its lining. It is an elastic tube which can dilate considerably. When not passing food, its mucous membrane is thrown into a number of irregular longitudinal folds (Fig. 194).

Liquids trickle very quickly through the esophagus. Solid food takes five or six seconds to be passed along by peristaltic action of the tunica muscularis. Gravity plays a part. Food passes much more slowly while you are lying down than while sitting up. In fact, the bolus may not quite make the grade if you attempt to swallow while upside down.

Mucosa and glands: The mucous membrane of the esophagus is lined with stratified squamous epithelium of the noncornified type in man and most other mammals. It becomes cornified in those animals which swallow rough vegetable matter. Papillae of the subjacent lamina propria indent the epithelium. The stratified epithelium ends abruptly, and simple columnar epithelium begins at the line of junction of the esophagus with the cardiac end of the stomach.

Glands are not numerous. Both superficial and deep esophageal glands empty mucus onto the surface epithelium by means of short ducts (Fig. 195). These ducts are dilated and lined with stratified squamous epithelium near the surface, but their branches become simple columnar epithelial tubes. The **deep esophageal glands** are tubulo-acinous. They occur in the submucosa as well as lamina propria. The **superficial esophageal glands** are branched tubular and are restricted to the lamina propria They closely resemble the cardiac glands of the stomach, adjacent

FIGURE 195 Human esophagus; a detail showing the following layers: 1, stratified squamous epithelium; 2, lamina propria; 3, muscularis mucosa; 4, submucosa containing a deep esophageal gland with a duct (*d*) in cross section, 5, inner circular layer of the muscularis. Photomicrograph, 125 ×.

to which they are numerous; they are also found farther up the esophagus.

The lamina propria is less cellular than that of most parts of the digestive tract. Occasionally, lymphatic nodules are encountered.

The muscularis mucosae is prominent at the lower end of the esophagus. It is often indistinct at the upper end, where it blends with a fibro-

esophageal

cardiac glands

submucosa

muscularis

gastric epithelium

FIGURE 196. Junction of esophagus and cardiac portion of a dog's stomach marked by an arrow. The esophagus with deep glands is above, the stomach, below Photomicrograph, 15 ×.

elastic lamina of the pharynx. The muscularis mucosae is made up of numerous closely placed bundles of smooth-muscle fibers arranged longitudinally.

Submucosa: The submucosa is thick. Its fibrous connective tissue contains many elastic networks.

Muscularis: Two muscular layers are distinct in the esophagus. The upper one-third of the muscular coat is formed mainly by the skeletal variety. This is especially true of the outer longitudinal layer, which is really a continuation of the inferior constrictor muscle of the pharynx. Some skeletal-muscle fibers may be found farther down the tube, but they are almost always absent in the lower one-third. A well-developed intermuscular nerve plexus containing ganglia is present.

Adventitia: This coat consists of rather dense fibrous connective tissue blending with the mediastinum, the partition dividing the thorax into halves, in which the esophagus courses. Where the esophagus passes through the diaphragm, it acquires a mesothelial covering for 1 or 2 cm. Many nerve fibers, notably the vagus nerves, course in the adventitia.

STOMACH

The stomach is a tubular organ when empty and is less of a sac than illustrations in gross anatomy books lead you to believe. Its distensibility is great, as you may be aware. Its functions are mechanical and chemical. Muscular movements churn its contents. Gastric juice, secreted by millions of tiny glands, provides chemical substances to liquidify and begin to digest food. The pulp-like stomach contents, known as **chyme,** are spurted into the intestine in small portions, beginning fifteen or twenty minutes after food has been swallowed.

The stomach possesses other functional capacities. It has a limited power to reject harmful substances by initiating vomiting. *By its secretion of large quantities of fluid, it can dilute them.* Its surface epithelium possesses noteworthy powers of regeneration.

The gastric juice is a pale colorless fluid containing about 0.4 to 0.5 per cent **hydrochloric acid** and several enzymes, chief of which is the proteolytic enzyme, **pepsin.** Gastric juice is formed in surprisingly large quantities; between 1 and 1.5 l. are produced daily.

Several parts of the stomach are distinguishable grossly. These are the **cardiac portion,** with its dilatation, the **fundus,** and the narrower lower **pyloric portion.** Differences can be observed between the microscopical structure of the gastric mucosa at the cardiac orifice, the pylorus, and the rest of the lining. The difference in structure between the fundus and the pylorus is well marked.

FIGURE 197. Gastric mucosa, *A*, fundus, *B*, pylorís: *a*, acidophilic parietal cell of a gastric gland, *m*, muscularis mucosa, the inner layer of which sends extensions into the lamina propria; *n*, mucous neck cells; *p*, gastric pit. Compare *A* with Fig. 198 and *B* with Fig. 199. 300 ×.

Mucosa: The mucous membrane of the stomach is thick, measuring as much as 1.5 mm. It is folded longitudinally into ridges, called **rugae**, which disappear to a large extent when the organ is distended. The lining is beset with numerous tiny **gastric pits** which are the openings of the ducts of glands of the stomach. From three to seven secreting tubules empty into each of these.

The **lamina propria** is scanty between gastric glands. It is more prominent beneath the surface epithelium and between the gastric pits. In addition to the usual reticular cells and lymphocytes, the lamina propria contains some smooth-muscle fibers. A muscularis mucosae is found just below the bottoms of the glands. This may be two layers of smooth muscle, as seen in Fig. 197.

The **surface epithelium** and that lining the gastric pits are simple columnar and are formed by mucous cells whose appearance varies somewhat according to the state of secretory activity (Fig. 200A). These cells constantly pour out mucus, which forms a thin layer over the surface for protection as well as lubrication. Whether this aids in the prevention of autodigestion of the mucosa by gastric pepsin is unknown.

The glands of the stomach are of three kinds: cardiac, principal, and pyloric. The principal glands, often called gastric glands, occur most extensively.

The **cardiac glands** are confined to a very small region, not more than 4 cm. away from the opening of the esophagus; often they are not seen at all. They resemble the superficial esophageal glands. Their cells secrete mucus, appearing first as mucigen. Droplets of mucus crowd the nucleus to the base of the cell near the basement membrane (Fig. 200B).

The **principal glands** are the most interesting. They are the glands that produce the hydrochloric acid and the proteolytic enzyme, pepsin—the substances that characterize gastric juice. They are tubular glands, each having a neck, or constricted portion, connecting with the bottom of a gastric pit. The body of each gland is a straight tubule ending blindly. The blind end is deep in the lamina propria upon the muscularis mucosae. Branching and bending may occur near it (Fig. 197A).

The cells that line the principal glands are simple columnar. Three types of cells are usually described.[1] Mucous cells occupy a limited region in the neck of the gland. These are designated **mucous neck cells**

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[1] A fourth type whose granules have affinity for silver salts, also present in the small intestine, may be related to pro   "
are scarce.

(Fig. 197A). They add their secretion to that of the surface mucous cells and pit mucous cells.

The **chief cells** of the glands, also called **peptic cells**, are the most numerous. They secrete pepsin. The secretion antecedent, pepsinogen, ap-

FIGURE 198 Fundus of the stomach of a 17-year-old girl. Specimen from Prof. A. J. Ramsay. Photomicrograph, 125 ×.

pears as granules in the cytoplasm but cannot often be seen without special staining methods. These granules are illustrated in Fig. 200C. In routine preparations, they are dissolved, in their place, you may see minute vacuoles in the cytoplasm. Nuclei of the chief cells are basally placed. The cytoplasm at the bottom of the cell stains with basic dyes and shows faint striations (Fig. 200C). Besides pepsin, other enzymes, notably rennin, may be formed by the chief cells.

The **parietal cells** are rather large swollen or ovoid cells with centrally

FIGURE 199. Pylorus of human stomach. Photomicrograph, 125 ×.

located nuclei (Figs. 197 and 200C). Their cytoplasm is only faintly granular and is strongly acidophilic. It may contain intracellular canaliculi (Fig. 29C). Parietal cells are most numerous in the upper half of
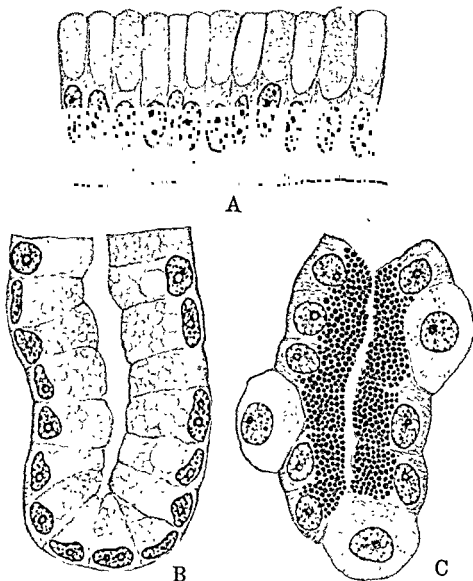
FIGURE 200. Gastric mucosa, showing details of A, surface epithelium; B, cardiac gland, C, fundic gland. 1200 ×.

the glands More deeply, they are crowded by the chief cells and occasionally appear to be hanging onto the outer surface of each gland (Fig 200C). Parietal cells secrete hydrochloric acid, which originates in the cell as an antecedent substance. The very striking appearance of parietal cells is the most characteristic diagnostic feature of the cardiac portion, fundus, and body of the stomach.

The **pyloric glands** are confined to the region of the pyloric canal and sphincter and are quite unlike the principal glands, for they are shorter,

FIGURE 201. Junction of a dog's pyloris with the duodenum, at the arrow. Photomicrograph, 15 ×

more branched, and coiled (Figs. 197B and 199). They, too, open into gastric pits. In the pyloric canal, they possess some parietal cells, but these disappear near the pyloric sphincter, and the glands come to be

lined with a single layer of columnar epithelium whose cells have clear cytoplasm and basally placed nuclei. They secrete no enzymes worthy of note but are mucous cells much like the mucous neck cells of the principal glands.

Submucosa: The tunica submucosae is formed of dense fibrous connective tissue containing a few fat cells. In it are the usual blood vessels, lymphatics, and the submucous ganglionated autonomic plexus.

Muscularis: The muscular coat of the stomach differs from that of other tubular digestive organs. It has three layers. An inner layer, arranged obliquely, has been added to the usual circular and longitudinal layers. The circular muscle is thickened at the pylorus to form the pyloric sphincter and diminishes in size abruptly at the junction with the duodenum No true cardiac sphincter is formed, although the inner oblique muscle is thickest at that end of the stomach. An intermuscular myenteric nerve plexus is well developed.

Serosa. A thin layer of visceral peritoneum, formed by fibrous connective tissue and mesothelium, covers the stomach and passes onto the **omentum.**

SMALL INTESTINE

The small intestine is a long glandulomuscular tube extending from the pylorus to the cecum. Its three subdivisions. **duodenum, jejunum,** and **ileum,** merge gradually into one another and present minor structural differences. Most of the small intestine is attached by a **mesentery (page 214)** to the body wall; otherwise it is free to move about in the abdomen Proper function is dependent upon this freedom. Since the intestine is not a storage depot, it is much less distensible than the stomach.

The small intestine differs sharply from the stomach in respect to structure of its wall, especially its mucous membrane. Instead of longitudinal rugae indented by pits, it has circular folds studded with minute projections Glands to secrete the intestinal juice are plentiful. The structure of the small intestine fits it admirably for its digestive and absorptive functions It is illustrated with diagrammatic clarity in Fig. 202.

Mucosa: The mucous membrane of the small intestine is covered with simple columnar epithelium made up of absorptive and goblet cells. The epithelium rests on a highly cellular lamina propria full of blood and lymphatic capillaries. A muscularis mucosae marks its junction with the fibrous submucous coat. The mucous membrane covers transverse folds

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of the submucosa, forming the **plicae circulares.** These folds are not ironed out by distention of the intestine but are permanent.

The absorptive surface area is very significantly increased by an infinite number of minute projections, the **intestinal villi,** the most characteristic
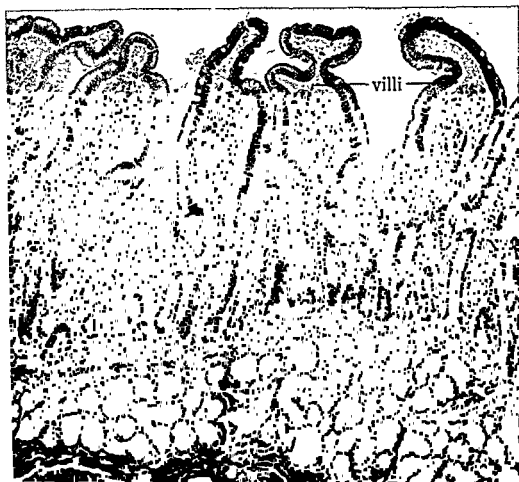
FIGURE 203 Human duodenum, *showing the mucous membrane with its villi and intestinal glands* (*i gl*) *and the submucosa with the duodenal glands* (*d gl*). Specimen by Prof. W. H. F. Addison Photomicrograph, 125 ×.

feature of the small intestine. All regions of it possess these structures, and no other part of the digestive tract has them. When the opportunity presents itself, examine villi with a hand lens in a freshly killed animal. These absorptive fingers of the mucosa vary in shape and density of population. They are broad and numerous at the upper end where digestion and absorption are most active. Toward the lower end, they are long, thin, and less numerous. Compare them in Figs. 203 and 204.

Villi are not static projections They are able to move actively, like the
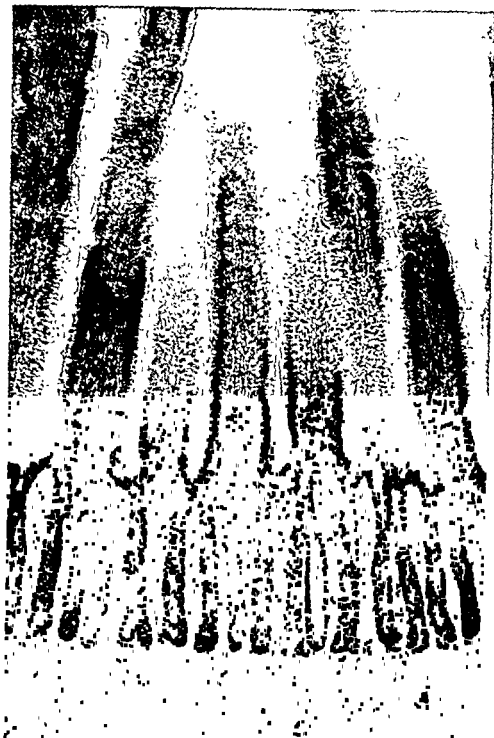
FIGURE 202 Small intestine of a kitten. Above the arrow, seven villi extend into the lumen of the intestine; below the arrow, sixteen intestinal glands are embedded in the lamina propria and rest on a thin muscularis mucosae, *m*, the submucosa, *s*, is seen at the bottom of the figure. Specimen in the Piersol collection Carmine stain. Photomicrograph, 150 ×.

granules in the cytoplasm between nucleus and free surface. These are the cells of Paneth. The nature of their granules, which are made bright pink by staining, is unknown. Other types of cells, *e.g.*, those mentioned in the footnote on page 290, are not ordinarily seen.

Intestinal juice, a yellow alkaline fluid, is secreted by the intestinal
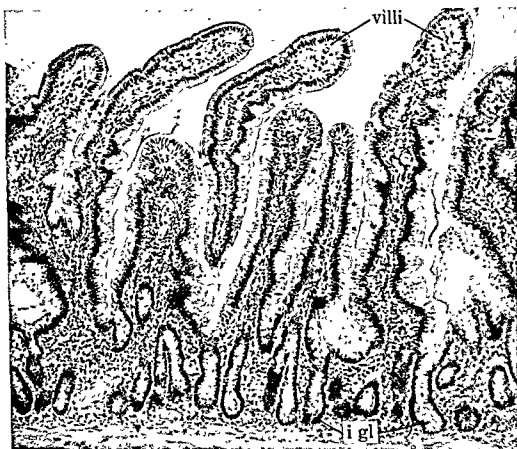
FIGURE 204 Human jejunum, showing tall villi and short intestinal glands (i gl) of the mucous membrane. Specimen by Prof W H F. Addison Photomicrograph, 125 ×.

glands. To it are added the secretions of the duodenal glands, pancreas, and liver. Intestinal juice contains a number of important digestive enzymes which break down protein and fat into components that can be absorbed by the surface epithelium. It is impossible to say which cells are responsible for secreting each enzyme. Nor do we know where in the duodenum the hormones **secretin** and **cholecystokinin,** which can induce flow of pancreatic juice and bile, are formed.

The **lamina propria** of the intestinal mucosa is well marked. It fills in between intestinal glands and extends into the villi. It is formed of re-

tentacles of a sea anemone, in the fluid intestinal contents, because each possesses a few smooth-muscle fibers in its core of lamina propria. Not only do the villi shorten and lengthen; they also swing from side to side.

The **surface epithelium** of the intestine is constantly undergoing renewal. Whole sheets of it are said to be sloughed in the normal course of events. Regeneration takes place with amazing rapidity from epithelium of the intestinal glands. Denuded intestinal villi, seen in most histological sections of human material, may signify post-mortem autodigestion rather than normal sloughing. The villi shown in Figs. 203 and 204, fixed in situ by suicidal swallowing of a solution of formaldehyde, have intact epithelium.

The surface epithelium is primarily concerned with absorption, but its many scattered goblet cells provide mucus to lubricate and protect it. Goblet cells increase in number toward the lower end. Mucus is important for the formation of feces.

The absorptive cells have their free surfaces graced by a striated border, as illustrated in Fig. 29A. Each absorptive cell is securely attached to neighboring cells at its striated border by means of some cement substance. This aids in the presentation of a continuous absorptive membrane to the intestinal contents.

The **process of absorption** is poorly understood. The absorptive membrane is readily permeable to water and to various salts and simple sugars in solution. Proteins are broken down into simpler molecules of amino acids before they pass into the cells. Fat is not absorbed as fat. It is broken into fatty acids and glycerol. These substances are passed through the absorptive membrane and immediately resynthesized into fat in the cytoplasm of the absorptive cells. Alteration of cytoplasmic organoids, principally the mitochondria, associated with fat absorption has been observed. How the intracellular fat droplets pass into the subjacent blood and lymphatic capillaries is unknown.

Intestinal glands, formerly called crypts of Lieberkühn, are unbranched tubes lined with simple columnar epithelium which is not quite so tall as the surface epithelium. They open onto the surface at the base of the villi (Fig. 202). Their cells are concerned with secretion of the intestinal juice and play no part in absorption. Consequently, they lack absorptive striated borders. Replacement of surface goblet and absorptive cells occurs at the upper ends of the glands by mitotic cell division and by movement of cells out onto the surface.

The cells at the bottom of the glands have prominent eosinophilic

Muscularis: The muscular coat consists of two well-formed layers of smooth muscle separated by a little fibrous connective tissue. The inner layer is circular, not spirally arranged as claimed by some. The outer one is longitudinal. Between the two layers is the prominent myenteric plexus.

The musculature of the small intestine serves to agitate food and digestive juices, facilitating the chemical reactions and enhancing absorption of water and the products of digestion. The musculature also propels the contents by a series of nicely coordinated peristaltic movements.

Serosa: The small intestine is covered by a thin layer of fibrous connective tissue, upon which a mesothelium is placed. This visceral peritoneum is reflected onto the mesentery along the line of its attachment to the intestine. Most of the duodenum lacks a mesentery and has only a partial serous coat.

LARGE INTESTINE

The large intestine is a spacious and somewhat sacculated tube for temporary storage and concentration of the digestive residue. In it, water is absorbed and the feces are formed. It may be subdivided into **cecum, colon,** and **rectum.** The vermiform **appendix** is an appendage of the large intestine. The usual four tunics are present, but they differ from those of other parts of the digestive tube.

Entrance to the cecum is guarded by the **ileocecal valve,** consisting of two flaps of mucosa. Muscles of the small and large intestines are thickened there and overlap to form a sphincter. Valve and sphincter release intestinal contents into the cecum and tend to prevent flow in the reverse direction. A sharp line of transition marks the junction of the mucous membranes of small and large intestines.

Mucosa: The outstanding difference between mucous membrane of the small and of the large intestine is absence of villi and lack of plicae circulares in the latter. Nevertheless, this notable reduction in surface area does not prevent quantities of water from being absorbed in the large intestine. The surface epithelium is smooth and formed by simple columnar cells. These cells are absorptive and have thin striated free borders. Goblet cells are present among them. Sloughing of surface epithelium occurs, and regeneration is effected from cells at the necks of glands. The structure of the colon is illustrated in Fig. 205.

Intestinal glands are deeper than those of the small intestine. Goblet

ticular connective tissue containing delicate elastic networks enmeshing many free cells. Its reticular fibers form the basement membrane of the intestinal epithelium and intestinal glands. Lymphocytes are its principal cells, although eosinophils, plasma cells, and mast cells are also numerous. The lymphocyte population varies greatly. Cells escaping into the intestinal lumen are often seen in sections of the epithelium. Very many more may enter the lumen with epithelial sloughing.

Throughout the intestine, the lamina propria contains solitary lymphatic nodules. The smallest are confined to the lamina propria of one villus. The largest may bulge into the submucosa beneath several villi. Aggregate lymphatic nodules are found toward the lower end, especially in the ileum. They somewhat resemble small tonsils and can easily be seen with the naked eye. Look for them in the wall opposite the attachment of the mesentery. Aggregate lymphatic nodules are called Peyer's patches. Lymphatic nodules are inconstant structures, and the loose lymphatic tissue also waxes and wanes.

The **muscularis mucosae** of the small intestine consists of inner circular and outer longitudinal smooth-muscle layers. A few small bundles of muscle fibers extend into the lamina propria. The muscularis mucosae is traversed by ducts of the duodenal glands. In the duodenum, it builds the important sphincter of the bile duct.

Submucosa: The tunica submucosae of the small intestine is like that of the stomach but is somewhat firmer. It forms the cores of the permanent plicae circulares. A submucous nerve plexus, containing numerous small autonomic ganglia, is present. Some groups of fat cells may be encountered. The principal function of the submucosa is to convey blood vessels and lymphatic vessels to and from the mucous membrane.

The **duodenal glands** (Brunner) lie in the submucosa. They are largest in the upper end, diminishing in size and number farther down. They may be absent in the lower part of the duodenum, or they may extend into the jejunum for a little way. They are made up of many small lobules, 1 mm. or less in diameter, sending short ducts into some of the intestinal glands.

The secretory portions are formed by branched and coiled tubules of simple columnar epithelium. Their pale mucous cells have basally placed and often flattened nuclei. They resemble the pyloric gastric glands. Secretion goes on continuously in the duodenal glands. It is thin mucus and contains a proteolytic enzyme which becomes activated by hydrochloric acid from the stomach.

zone extends to the anal orifice where the skin begins. Hair, sebaceous glands, and apocrine sweat glands appear at the junction.

FIGURE 206. Anal canal of a child, longitudinal section Specimen in the Piersol collection. Photomicrograph, 14 ×.

The lamina propria and muscularis mucosae of the large intestine are similar to those layers in the small intestine.

Other tunics. The submucosa presents no unusual features in the

cells are so numerous in them that other types can scarcely be made out. The mucus produced by these glands, and by the few surface goblet cells, lubricates and protects the mucosa. It also aids in the formation of gradually dehydrated fecal masses and in their progression toward the descending colon and rectum.

FIGURE 205. Human colon, longitudinal section. Note absence of villi and presence of long intestinal glands filled with goblet cells. A sheet of mucus covers the surface epithelium. Photomicrograph, 125 ×.

The **epithelium of the rectum** possesses the longest intestinal glands, measuring up to 0.7 mm. in length, but they are fewer than elsewhere.

The lower portion of the rectum is the **anal canal**, illustrated in Fig. 206. In it, vertical folds of the mucosa form the **rectal columns**. These end about 15 or 20 mm. from the anal orifice by uniting in crescentic folds called **anal valves**. These valves enclose blind pockets, the **rectal sinuses**. In the anal canal, the intestinal glands stop, and the surface epithelium becomes noncornified stratified squamous. This transition

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ranged equidistant from one another. Contraction of these tends to throw the wall of the colon into a series of **sacculations**. The circular layer of muscle is thickened to form the **internal anal sphincter** in the anal canal. An external sphincter, outside of this, is formed by skeletal-muscle fibers.

A serous coat is present in most of the colon but absent from part of the rectum and the anal canal Attached to it are small pedunculated tabs of fat covered with mesothelium. These are **appendices epiploicae.**

APPENDIX

The small lumen of the appendix presents an irregular and angular form. Its mucous membrane has absorptive and goblet cells. Intestinal glands are relatively few and are irregular in shape. They are crowded with goblet cells.

The lamina propria is heavily infiltrated with lymphocytes. Lymphatic nodules, often breaking up the muscularis mucosae and penetrating the submucosa, may form a complete ring around the lumen. The submucosa contains fat cells. Both muscular coats are complete. The serous coat is continued onto a small mesentery.

The appendix is subject to inflammation and infection and may show marked departure from normal structure, even in subjects regarded as healthy. The lumen may be partly or completely obliterated. Occasionally the mucosa is replaced by fibrous connective tissue. Figure 207 shows a reasonably normal appendix.

BLOOD VESSELS, LYMPHATICS, AND NERVES

The mesenteries convey arteries and nerve fibers toward the digestive tube, and veins and lymphatic vessels away from it. A general plan prevails throughout each part. Freely anastomosing arteries are found everywhere. The villi of the small intestine impose interesting differences in the vascular and lymphatic arrangements.

The fibrous connective-tissue layers of the digestive organs provide convenient paths for the conduction of blood vessels, lymphatic vessels, and nerves and for the formation of networks and plexuses. The main network of blood vessels is found in the submucosa. Branches pass out to the muscular layers and in to the lamina propria of the mucous membrane. Secondary networks are formed in these locations, and capil-

ceecum and colon. That of the anal region contains sensory nerves and nerve endings of the pressure-receptor type.

human appendix Photomicrograph, 30 ×.

The muscularis of the human large intestine is formed by a strong inner circular layer and a partially deficient outer longitudinal layer. The outer layer has been reduced to three stout bands, the *taeniae*, ar-
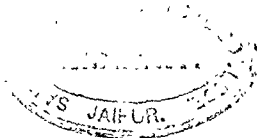
Liver and Pancreas

The liver and pancreas are the two largest glands of the body. Each of them is an outgrowth of the alimentary tube in the embryo. The liver, weighing about 1.5 kg., is at least ten times the size of the pancreas. It forms about one-fiftieth of the adult body weight. In the newborn infant, the ratio is approximately one to twenty. Its structure and its principal functions are unlike those of other exocrine glands. The pancreas resembles the serous salivary glands, but it has an important endocrine component added. The exocrine secretions of the two glands reach the duodenum by large ducts and contribute their enzymes to the intestinal fluid. The duct of the liver has an appendage, the gall bladder, in man and in some other species.

LIVER

The liver is a gland of many functions, and yet it displays remarkable simplicity of structure. Only one type of parenchymal cell is found in it. You will have no trouble with the liver if you understand its blood vessels. Of course, they run in connective tissue.

Stroma· Fibrous connective tissue forms a thin **capsule** (Glisson) which entirely invests the liver and is covered almost everywhere with mesothelium, making it the visceral peritoneum of the liver. The capsule may be seen in Fig. 208.

At a hilus, which is known as the **hepatic portal**, the capsule is thickened and extends into the liver to form an internal fibrous connective-tissue framework. The finest subdivisions of this stroma are made of reticular tissue. Larger trabeculae or **septa** incompletely delimit small subdivisions of liver parenchyma, known as **hepatic lobules**, which are little polyhedrons of liver substance about 1 mm. wide and 2 mm. high.

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lary plexuses abound among their elements. Venous networks are similarly disposed.

Each intestinal villus is provided with an arteriole or two, which break up into capillaries. The capillaries come to lie close to the epithelium, where they receive all absorbed materials except the major portion of the fat. Venules draining the villi are usually located on the side opposite the arterioles.

Lymphatic capillaries begin as blind channels. They are numerous in the lamina propria, where they collect tissue fluid and lymphocytes. They are joined by others to form larger vessels, which build networks in the submucosa. Each villus contains one or more centrally placed lymphatic capillaries, known as lacteals. The lacteals receive quantities of fat droplets during digestion and their fat-laden lymph is called **chyle.**

Nerves of the digestive tube are mostly autonomic. Two main plexuses are the **myenteric** and the **submucous plexuses.** Both of these contain many small ganglia of autonomic nerve cells. Some sensory nerve fibers and nerve endings occur in the digestive organs. They are relatively few compared with those of the surface of the body. You can feel very little in healthy abdominal viscera.

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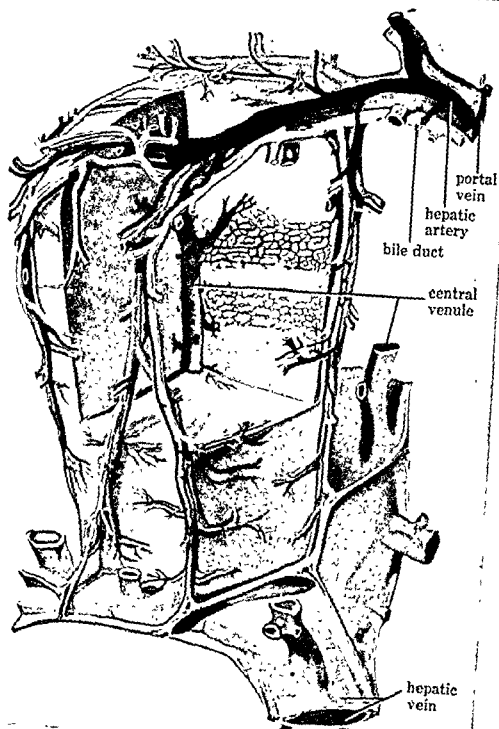
FIGURE 209 Reconstruction of a liver lobule of a pig, showing relation of blood vessels and bile ducts to liver parenchyma, modified from H Braus, *Anatomie des Menschen*, vol 2, Verlag Julius Springer, Berlin, 1924

Figure 209 shows a wax reconstruction of a partly dissected lobule in relation to its blood vessels and ducts.

Blood vessels: The liver is interposed in the path of the venous drain-
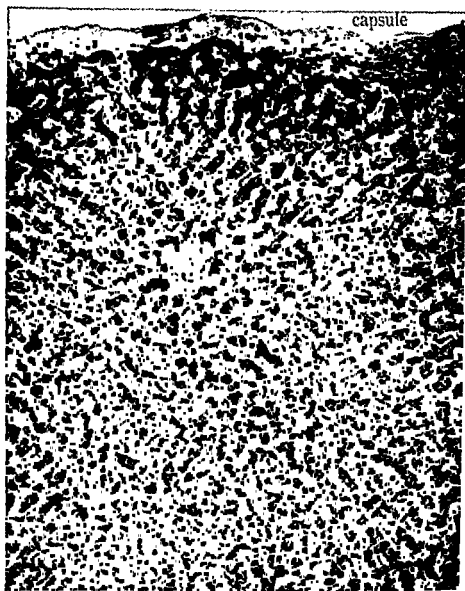
FIGURE 208. Human liver with fibrous connective-tissue capsule; one central venule is shown ($\circ$), radiating from it are hepatic cell cords and hepatic sinusoids. Photomicrograph, 150 $\times$.

age from the intestines. Its main afferent vessels are branches of the **portal veins.** An auxiliary blood supply is provided by small **hepatic arteries,** which are confined to the connective tissue and serve mainly to nourish the biliary system. Since both of these subdivide repeatedly and course among the hepatic lobules in the septa, their branches are sometimes designated interlobular. From **interlobular venules** (some from the

its center. There they come together and enter a **central venule** which occupies the core of the lobule (Fig. 208). Central venules from several lobules join to form tributaries of the hepatic veins. These tributaries
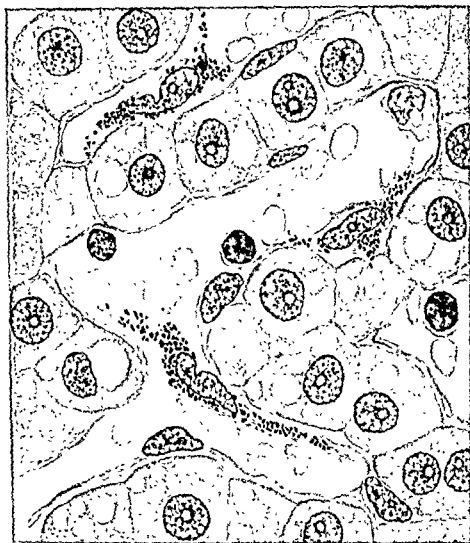
FIGURE 211. Hepatic sinusoids, showing endothelial cells and macrophages lining them. 1200 ×.

may be designated **sublobular veins** after they leave the hepatic lobules. **Hepatic veins** ultimately drain into the inferior vena cava.

Lymphatics. Lymphatic vessels are very numerous in the capsule and the interlobular connective-tissue septa (Fig. 210). The important fact about them is that they do *not* enter the lobules. Nevertheless, a great quantity of lymph, which is rich in proteins, leaves the liver. Much tissue fluid filters from the liver parenchyma through the intercellular spaces

arterioles, too), an apparently infinite number of tiny short branches arise, and these immediately spread out into the vast networks of hepatic

FIGURE 210 Hepatic vessels and ducts in interlobular connective tissue: *a*, hepatic arteriole, *h*, bile ductules, *l*, lymphatic vessels, *v*, portal venules containing blood corpuscles 900 ×.

sinusoids in the liver parenchyma. Interlobular venules and a hepatic arteriole are seen in Fig. 210.

Sinusoids filter blood through the hepatic lobule, converging toward

In the cytoplasm of the hepatic cell are seen fat and glycogen droplets when proper technical procedures are employed (Fig. 7). Glycogen is formed in the hepatic cells from glucose brought by the portal blood stream from the intestines. It is stored in the liver and given up again as glucose to the sinusoidal blood stream upon demand. Fat and protein also can be converted into glycogen by the hepatic cells. Storage of glycogen begins in the cells nearest the central venules and extends gradually outward toward the periphery of the lobule. When glycogen is given up to the circulation, the outermost cells of the lobule are depleted first.

The hepatic cells form urea in the process of protein metabolism. This chemical is then transported to the kidney by the blood stream. The liver's role in excretion is essential.

Fat storage in the liver is important. A number of other things besides glycogen and fat are stored there, too. These include vitamin A.

The liver plays an important role in the mechanism of blood clotting. The hepatic cells form fibrinogen. While considering liver functions, do not fail to recall its capacity in the embryo to produce blood corpuscles.

Bile is the exocrine secretion of the liver. Biliary pigments are produced from hemoglobin derived from red corpuscle destruction elsewhere but excreted in the liver. Some of the other bile constituents are secreted by hepatic cells.

Bile capillaries are illustrated in Fig. 212A. They always lie between hepatic cells. As they pass toward the periphery of the hepatic lobule in the cell cords, they anastomose extensively. Many are collected into larger channels at the interlobular connective-tissue septa, draining there into the interlobular bile ductules The bile capillaries have no true walls of their own, but the hepatic cells form their walls.

Bile ductules always accompany interlobular portal venules and hepatic arterioles. These triads—ductule, venule, and arteriole—are seen at the places where several hepatic lobules join (Fig. 210). The smallest bile ductules are lined with low columnar epithelium continuous with the hepatic cords but made of smaller nonsecretory cells. The smallest bile ductules may give rise to hepatic cells during regeneration after liver damage. The epithelium becomes thicker in the larger ductules and is surrounded by connective tissue.

of the parenchymal reticular tissue to reach the lymphatic vessels of the interlobular connective-tissue septa.

Parenchyma: Hepatic sinusoids, hepatic cells, and bile capillaries make up the **liver lobule.** It is the unit of the liver structure and function (Figs. 208 and 209).

The sinusoids are wide capillaries among cords of hepatic cells, carry-
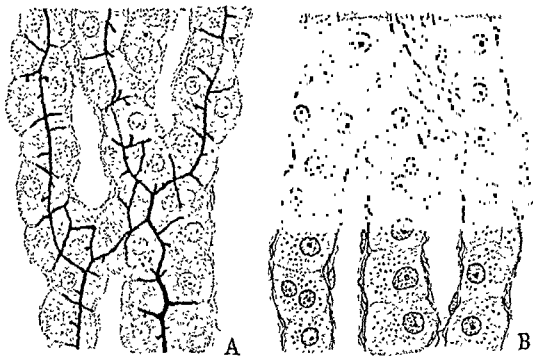
FIGURE 212. Hepatic cell cords. Bile capillaries are blackened with silver in A. Reticular fibers around hepatic cells are stained by the silver carbonate method in B 900 ×.

ing blood from portal to hepatic (central) venules They are lined by two kinds of cells. One is typically endothelial, but the other is a macrophage with processes sticking it to the sinusoidal walls. These stellate macrophages,[1] illustrated in Fig. 211, phagocytize foreign particles and worn-out red blood corpuscles. There are more macrophages in the liver than anywhere else in the body. Thus, the liver is a blood filter of prime importance.

The **hepatic cells** are arranged in cords (some say they form plates), which anastomose and branch as they radiate from the central venules. An irregularly double row of cells forms each cord, and a bile capillary is sandwiched in between (Fig. 212A). Individual hepatic cells are polyhedral and contain one or two nuclei (Fig. 6A).

[1] Macrophages of the liver sinusoids are called cells of Kupffer.

muscle to encircle the ductus choledochus, as well as the pancreatic duct, forming separate sphincters for each and a common one, known as the sphincter of Oddi. The **sphincter choledochus** prevents bile from flowing into the intestine during fasting. The sphincter is caused to relax by ingestion of food, but at other times it is closed tightly and this causes bile to back up into the gall bladder.

The **gall bladder** holds a variable quantity—50 cc., more or less—of bile, storing it between meals and absorbing water from it. In structure, it resembles the tubular digestive organs but lacks a tunica submucosa, and the other layers are thin. The lining is extensively folded, and some of the folds remain during marked distention of the organ. The neck of the gall bladder continues into the cystic duct, where folds are especially prominent, forming the **spiral valve** (Heister).

The mucous membrane of the gall bladder consists of a layer of tall simple columnar epithelium resting on a lamina propria (Fig. 213). The epithelium lacks goblet cells, and a striated border can be observed upon it only occasionally (Fig. 22), although the cells are concerned with absorption. There are glands in the gall bladder only at its neck. There, the lamina propria contains a few very small tubulo-acinous glands secreting mucus

The muscularis of the gall bladder is irregular. The inner layer contains longitudinal fibers, and the outer layer is roughly circular. Some fibers course obliquely.

A thick perimuscular connective-tissue layer intervenes between muscularis and serosa. Blood vessels and nerves course in it. The nerves are autonomic, providing innervation of the muscle. Other nerve fibers are sensory, but they ordinarily do not convey messages that are perceived. Lymphatics join those draining the liver.

The gall bladder empties during digestion of fat by contraction of its musculature. This can occur in the absence of a nerve supply and can be induced by the hormone **cholecystokinin**, formed in the duodenal mucosa.

PANCREAS

The pancreas has a great deal to do with regulating blood sugar concentration and with carbohydrate digestion. It is really two organs. One is a tubulo-acinous exocrine gland, resembling the parotid The other portion is endocrine, formed by many pancreatic islands (Langerhans), which are embedded in the exocrine gland (Fig 214).

BILE DUCTS AND GALL BLADDER

Bile ductules come together to form larger ducts, and these assemble to form the left and right **hepatic ducts.** They, in turn, join in construction of a common hepatic duct. This leaves the hepatic portal, carrying

FIGURE 213. Gall bladder of a cat. Photomicrograph, 150 ×.

bile to the gall bladder to be condensed. The **cystic duct** of the gall bladder and the common hepatic duct unite, and the resulting **ductus choledochus,** or bile duct proper, passes to the duodenum. As this duct courses obliquely through the duodenal wall, it is first accompanied and then joined by the main pancreatic duct.

All the ducts are lined with tall simple columnar epithelium. In the larger ducts, circular and longitudinal smooth-muscle fibers are irregularly disposed in dense fibrous connective tissue to complete the structure of the wall.

The muscularis mucosae of the duodenum contributes bands of smooth

The acini of the pancreas are purely serous. Their pyramidal cells have a characteristic two-toned appearance with hematoxylin and eosin dyes. They are slightly striated and stain blue at the base. Apically, they stain pink. Zymogen granules in the apical cytoplasm can be demonstrated with appropriate techniques. These granules appear and disappear with fasting and digestion.

FIGURE 215 Centroacinar cells in the pancreas of a guinea pig. Redrawn from R R Bensley, *American Journal of Anatomy*, vol. 12, 1911.

Secretion accumulates during fasting. It is poured out in response to the hormone **secretin**, which is liberated from the duodenal mucosa by gastric hydrochloric acid and bile acids at the beginning of intestinal digestion.

The acini contain a few centrally placed low columnar or squamous cells protruding into their lumen. These are the nonsecretory **centro-acinar cells** (Fig. 215). They represent the beginning of the pancreatic duct system. To a varying extent, each acinus folds around its **interca-lated duct**, often bulging to one side like a boxing glove over the hand and wrist.

Intercalated ducts have flattened epithelium They are long and branched. No secretory ducts are present in the pancreas. Long inter-calated ducts enter interlobular ducts directly. All excretory ducts are

The pancreas is surrounded by much loose fibrous connective tissue. This forms no definite capsule, but septa carrying blood vessels, lymphatics, and nerves divide the gland into many lobules. Lamellated cor-
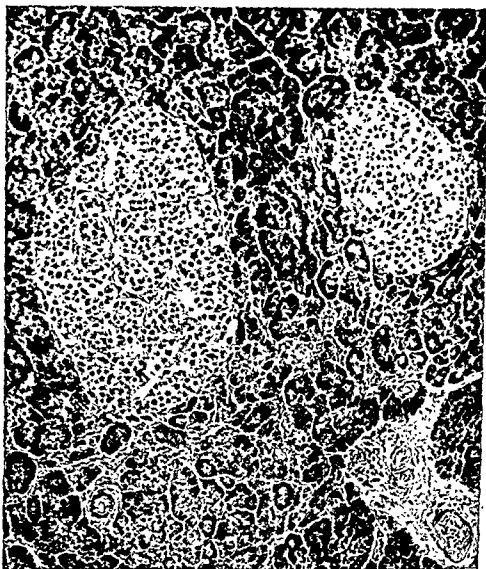
FIGURE 214. Human pancreas, showing two islands. Note the small duct below the larger island and the connective tissue with blood vessels below the smaller island. Compare with Fig 189 Photomicrograph, 150 ×.

puscles (Pacini) are commonly encountered in the connective tissue of the pancreas.

Exocrine pancreas: The pancreas produces an alkaline secretion containing trypsin, lipase, and amylase, enzymes that split proteins, fat, and starch into simpler compounds for absorption. If there are specific pancreatic cells secreting each of these enzymes, we cannot identify them.

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lined with tall simple columnar epithelium and are surrounded by fibrous connective tissue.

The main pancreatic duct and an accessory pancreatic duct have thick coats of dense fibrous connective tissue. Their epithelium contains goblet cells, and a few tiny mucous glands may be encountered in their walls.

Endocrine pancreas: The endocrine portion of the gland consists of **pancreatic islands** (Langerhans) that vary in size from groups of a few cells to masses 0.5 mm. or more in diameter. They are slightly more numerous in the tail than at the head of the gland. Some thin strands of cells, related to the islands, have been described.

The islands have a rich blood supply, as you might expect of a gland of internal secretion. Large capillaries come into close relation to cords of epithelioid cells. Cords lack lumens, the secretion passing directly into the blood of the capillaries. This is the fundamental plan of an endocrine gland.

You will see little differentiation of cell types in the pancreatic islands with routine staining (Fig. 214). However, special techniques have revealed differences, and three kinds of cells have been observed. These are designated **A, B,** and **D cells,**[2] but the significance of each is poorly understood. The B cells are the most numerous. All three types are lighter in hematoxylin and eosin preparations than cells of surrounding acini. Granules can be observed in their cytoplasm, but only with special stains.

The secretion of the pancreatic islands is **insulin**. It appears to be formed mainly by the B cells. Its function is regulation of the blood sugar level. Deficiency of insulin leads to an increase in the amount of sugar entering the blood, and this is accompanied by excretion of sugar in the kidney. Deficiency occurs in **diabetes mellitus**. The conquest of this disease, culminating in the successful isolation of insulin by Banting and Best,[3] is a subject that will hold your interest over some spare week end.

REFERENCES

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   Professor Bensley has added important details to knowledge of the liver cell in this short recent article.

2 Another, *C cell,* is present in the guinea pig

3 *Journal of Laboratory and Clinical Medicine,* vol. 7, 1922.

2. Hard, W. L.: The Origin and Differentiation of the Alpha and Beta Cells in the Pancreatic Islets of the Rat, *American Journal of Anatomy*, vol 75, pp. 369–403, 1944.
This development study will show you another type of experimentation and at the same time give you more information about the very important endocrine component of the pancreas.

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and tissue fluids, but most of them are picked out by some specific organ or by a limited group of cells and do not affect all organs indiscrimi-
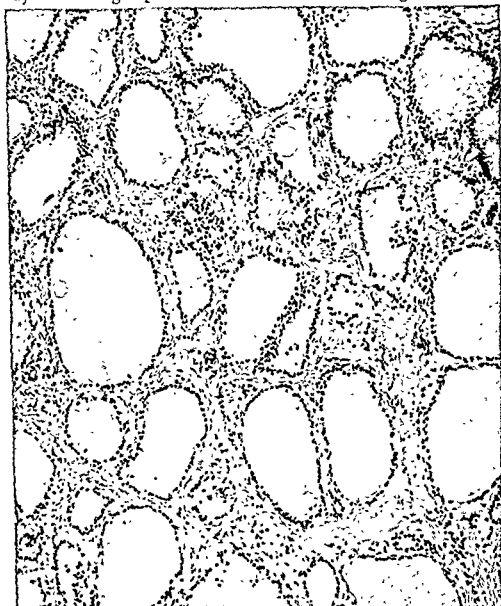
FIGURE 218 Human thyroid gland Follicles are filled with colloid during life, and the few vacuoles seen here are artifacts Photomicrograph, 150 ×

nately. Thus, each endocrine gland becomes related to other endocrines or to some nonendocrine organ, for which it serves as regulator.

THYROID GLAND

The thyroid gland, weighing only 20 or 30 gm. in man, nevertheless is the largest endocrine organ It lies in the neck, embracing the upper

Endocrine Organs

In this chapter we shall consider the glands of internal secretion, or endocrine organs. Although these do not comprise an anatomical system, they are rather closely related and interdependent functionally. Some are quite simple; others present a structure of considerable complexity. Embryologically, they arise from no one germ layer. They commonly develop as components of other nonendocrine organs. You have already observed such a relationship between the pancreas and its insular endocrine component.

The endocrine organs are ductless glands; *i.e.*, their parenchymal cells secrete substances that are passed into the vascular or lymphatic systems rather than into ducts. The secretions of some are referred to as **hormones** because they excite activity of other organs. They fall into several groups. Some stimulate activity of smooth muscles, others regulate metabolic functions, and a third group has to do with controlling growth and development. Commonly, several active principles are formed in one endocrine organ, and it is seldom possible to relate specific parenchymal cells to them.

The internal secretions are not formed solely in the endocrine glands. Reference has been made to the production of secretin by the duodenal mucosa. The duodenum is certainly not primarily an endocrine organ. A number of sex hormones are secreted by the ovary and testis, organs with other important nonendocrine functions. We have mentioned the role of the liver in secreting glucose into the blood stream from its store of glycogen. This is not a hormone, although the process of its secretion resembles that of the endocrine glands.

A feature of endocrine secretion is that the active substances are made accessible to any and all cells of the body as they circulate in the blood.

FIGURE 218 Stroma of the thyroid gland, containing a small artery, *a*; veins, *v*, and lymphatics, *l*, as well as nerves, *n*. Note the valve in a vein. 100 ×

end of the trachea and lower part of the larynx. It is formed by two lateral lobes on either side of a connecting isthmus. A median pyramidal lobe lies in front of the larynx in about one-third of all individuals.

The **stroma of the thyroid** is formed by fibrous connective tissue. In the finer subdivisions of this tissue, reticular fibers are numerous. The
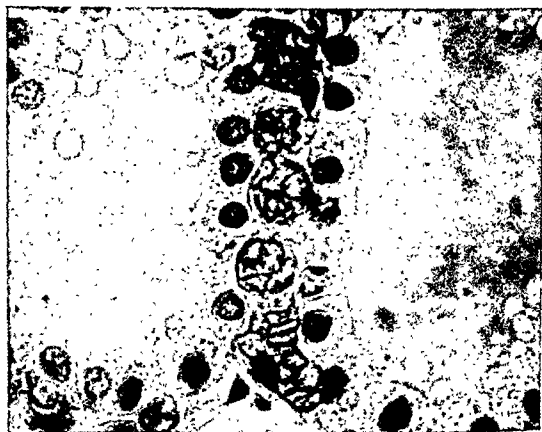
FIGURE 217 Thyroid of a rat, showing a row of greatly distended blood-filled capillaries between the walls of two adjacent follicles Specimen by Mr. B B. Varian. Photomicrograph, 1200 ×

gland is encapsulated by part of the deep fascia of the neck. From the capsule, trabeculae pass into its substance, subdividing it into lobules and carrying the larger blood vessels and lymphatics as well as nerve bundles. The interfollicular stroma is mainly reticular and contains the remarkably rich vascular and capillary plexuses. No basement membranes are formed by the reticular tissue, but the capillaries are brought into close association with the glandular epithelium, as shown in Fig. 217. The stroma and the vessels and nerves running in it are illustrated in Figs. 218 and 219.

The **parenchyma of the thyroid** gland consists of innumerable tiny

There is only one type of cell recognizable in the follicular epithelium. It is almost cuboidal in shape, but shape and size vary somewhat with age, sex, and the state of thyroid activity. Cell division is rare. Degenerating cells occasionally appear. The structure of thyroid epithelium is seen in Fig. 217.

The direction of secretion of thyroid follicle cells is into the lumen. Secretion droplets have been seen pinching off at the free cell surface, as in apocrine glands. The thyroid secretion is stored in the colloid and reabsorbed into the blood stream through the epithelium as needed. This reabsorption is made possible by hydrolysis of the colloid by a proteolytic enzyme. Intense hyperactivity during abnormal conditions leads to the speeding up of the processes of secretion into the colloid, its hydrolysis, and reabsorption.

The primary function of thyroid secretion is regulation of the metabolic rate of the body. Hypofunction leads to the slowing down of metabolic processes. This is manifested in the thyroid by increased amount of colloid and reduction in height of epithelial cells. Hyperfunction causes an increase in the basal metabolic rate. The thyroid follicles are depleted of colloid, and the epithelium becomes taller and sometimes folded. Hypertrophy of the epithelium may occur during marked hyperactivity.

An interrelationship exists between the thyroid and other endocrine glands. Most notable is the stimulation of thyroid secretion by a **thyrotropic hormone** from the anterior lobe of the hypophysis. The thyroid is sensitive to deficiency in iodine, an optimum quantity of which must be present in the diet to maintain normal thyroid function and structure.

PARATHYROID GLANDS

There are four parathyroid glands. Each one is a small body, measuring approximately 3 by 6 mm., located on the posterior surface of the lateral lobes of the thyroid gland close to the anastomosing superior and inferior thyroid arteries. Occasionally, one or more accessory or aberrant glands may be present. The appearance of the parathyroid at low magnification is illustrated in Fig. 220.

The **parathyroid stroma** is inconspicuous. A fibrous connective-tissue capsule surrounds each gland and separates it from the thyroid. This gives rise to small trabeculae for the blood vessels that supply the parenchyma. The finer subdivisions of the stroma are reticular and carry the sinus-like capillaries.

globoidal cysts or **follicles** lined with low simple columnar epithelium. The follicles vary in size from small clumps of cells with scarcely any lumen to those measuring 100 to 200 μ in diameter. These are filled with
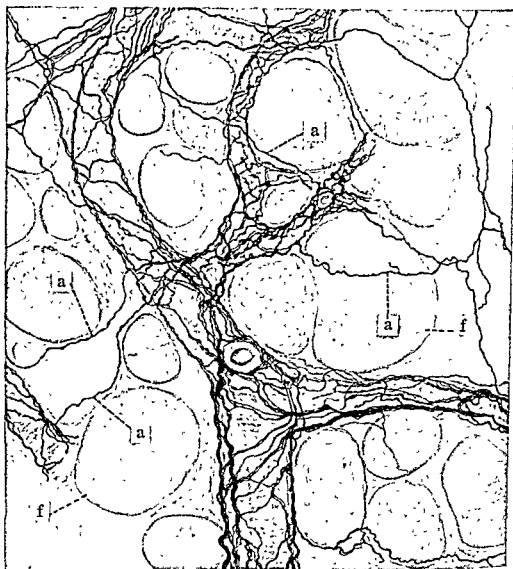
FIGURE 219. Nerves forming perivascular plexuses on arteries of a dog's thyroid gland: nerve fibers, *a*; thyroid follicles, *f*. Golgi stain.

a fluid substance known as **colloid**, which is rich in iodine and contains the **thyroid hormone.**

Colloid is usually found incompletely filling the follicles in fixed and stained preparations, where it has shrunken away from the epithelium (Fig. 216). It is usually acidophilic. Occasionally, detached epithelial cells or lymphocytes are seen in it. In life, the colloid completely fills the follicles.

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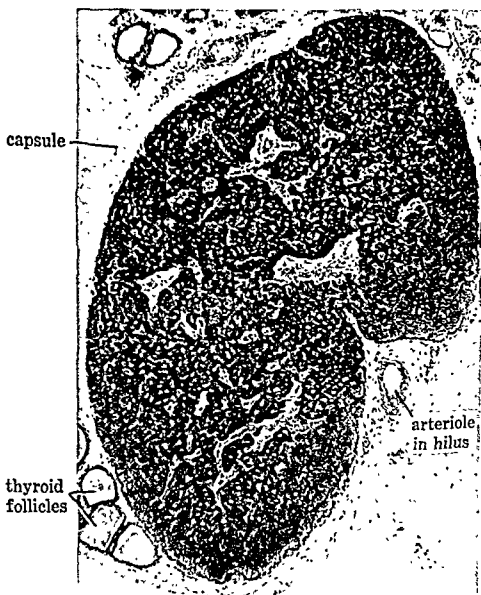
FIGURE 220. Parathyroid gland. Nonidez photomicrograph, approximately 80 ×.

are not the same as thyroid follicles. They have no unusual amount of iodine in them.

The cells of the parathyroid cords are of two types called **principal cells** and **acidophil cells.** The cytoplasm of the principal cells is pale and nongranular. That of the larger, acidophil cells is darker and con-

tains fine granules, which take the eosin stain. The acidophils have not been identified in man during the first ten years of life, and they are absent in some species of mammals. Figure 221 is from a human parathyroid gland and shows the two types of cells.

The cells secrete **parathyroid hormone,** which is concerned with regulation of calcium metabolism. Just how it serves to maintain the level
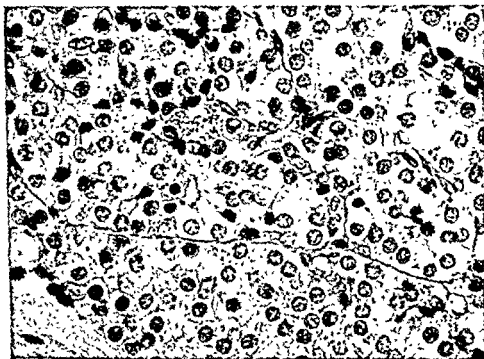
FIGURE 221. Human parathyroid gland The lumen of a pseudofollicle is seen a little to the left of the center. Two small dark nuclei on its immediate left belong to acidophil cells; larger, lighter nuclei belong to principal cells Photomicrograph, 600 ×.

of blood calcium we do not know. Parathyroid glands are essential for maintenance of life. Removal of them leads to development of parathyroid tetany.

SUPRARENAL GLANDS

The suprarenal glands form little caps for the rostral ends of the kidneys, from which they are separated by some fibrous connective tissue. The two suprarenal glands differ from the many pancreatic insular glands, the four parathyroids, and the single thyroid in respect to greater structural and functional complexity. Each, in reality, is a duplex organ, consisting of **cortex** and **medulla,** which form different secretions. Each

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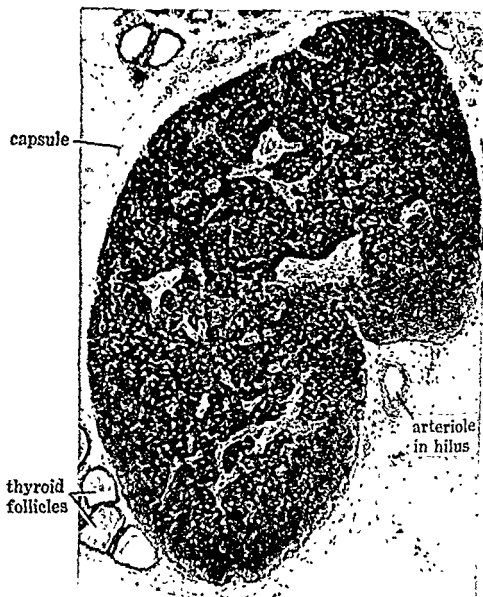
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places. There they enter the substance of the gland in delicate trabeculae from the capsule. Lymphatic vessels course beneath the capsule. The

FIGURE 223. Human suprarenal gland, showing fibrous connective-tissue capsule, zona glomerulosa, and a small part of zona fasciculata. Photomicrograph, 300 ×.

finest subdivisions of the trabeculae are formed of reticular connective tissue, as in the other endocrine organs you have studied. This reticular tissue supports the smallest arterioles, the capillaries of the cortex, and

gland weighs approximately 6 gm. Part of one gland is shown in Fig. 222.

The **suprarenal stroma,** with its blood vessels and nerves, is of major

FIGURE 222. Human suprarenal gland, showing its division into cortex, the darker peripheral region, and medulla, the lighter central area. The largest vein, *v,* is sectioned near the hilus, and cortical tissue indents the gland here to form an incomplete dark ring. Longitudinal smooth-muscle bundles lie inside this ring. Arteries, *a,* appear in the surrounding adipose tissue. Photomicrograph, 13 ×.

importance. A capsule of fibrous connective tissue covers the surface and passes into the gland at the hilus. From this point, there emerges a relatively large suprarenal vein, characterized by an abundance of longitudinally arranged smooth muscle. Arteries supplying the gland come from three sources. Their branches penetrate the capsule at various

suprarenal cortex of the fresh unstained gland. The narrow zona reticularis has both **light** and **dark cells.** The dark cells not only stain deeply;

FIGURE 224 Human suprarenal gland. The same specimen as Fig 223, showing zona reticularis on the left and medulla on the right Photomicrograph, 300 ×

they have some brown lipochrome pigment in their cytoplasm. They may be the old cells approaching physiological degeneration. Macrophages are found among the lining cells of the sinusoidal capillaries of the zona reticularis.

the sinusoidal capillaries of the medulla. The suprarenal gland has the richest supply of blood of all the organs in the body, although you will scarcely believe this when you see routine sections in which most of the capillaries are empty and collapsed.

Bundles of nerve fibers pass from the capsule of the suprarenal gland through the cortex to the medulla. Some fibers supply smooth muscle of the suprarenal blood vessels. However, most of these nerve fibers end among cells of the medulla. They are preganglionic sympathetic nerve fibers ending among gland cells instead of on postganglionic neurons.

Cortex of the suprarenal gland: The fundamental plan of the cortex is an arrangement of parallel cords of cells knotted and looped at the periphery and branched and anastomosing at their medullary ends. Blood capillaries, formed beneath the capsule, pass toward the medulla among the cords and are in intimate contact with their cells. When the cords branch and anastomose, the capillaries do likewise. All of the blood enters the suprarenal cortex at its periphery and leaves the cortex at its deep border. Consequently, a gradient may exist in respect to diffusion of substances out of and into capillaries, and it is not surprising to observe a marked change in the appearance of cells from the exterior toward the interior of the cortex.

Three principal zones can be distinguished in the cortex. *The outermost is the* **zona glomerulosa.** *There the cells are arranged in balls or loops at the ends of the cords. This is a narrow zone, as will be seen in Fig. 223. Straight parallel columns of cells, two thick as a rule, form the* **zona fasciculata.** *This is the widest. Cell cords anastomose in the narrow* **zona reticularis,** *which is innermost next to the medulla (Fig. 224). These anastomosing cords are usually only one cell thick.*

The elements of the cortical parenchyma are replaced by transformation of indifferent cells of the suprarenal connective-tissue capsule into new glomerular cells. Mitotic division of cells in the zona glomerulosa push newly formed cells inward. Mitoses are not confined to the peripheral region but may be seen in the zona fasciculata, too. Cells of the zona reticularis once occupied a peripheral position. Some cells will be found undergoing degenerative changes in the zona reticularis.

Cells of the zona glomerulosa stain darkly. *They have deeply staining nuclei and some basophilic material in the cytoplasm. Those of the zona fasciculata are characterized by numerous cytoplasmic lipoid droplets, indistinguishable as such in fixed and stained preparations but represented by vacuoles. This lipoid material imparts a yellowish color to the*

suprarenal cortex of the fresh unstained gland. The narrow zona reticularis has both **light** and **dark cells**. The dark cells not only stain deeply;

FIGURE 224 Human suprarenal gland. The same specimen as Fig. 223, showing zona reticularis on the left and medulla on the right. Photomicrograph, 800 ×.

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The elements of the cortical parenchyma are replaced by transformation of indifferent cells of the suprarenal connective-tissue capsule into new glomerular cells. Mitotic division of cells in the zona glomerulosa push newly formed cells inward. Mitoses are not confined to the peripheral region but may be seen in the zona fasciculata, too. Cells of the zona reticularis once occupied a peripheral position. Some cells will be found undergoing degenerative changes in the zona reticularis.

Cells of the zona glomerulosa stain darkly. They have deeply staining nuclei and some basophilic material in the cytoplasm. Those of the zona fasciculata are characterized by numerous cytoplasmic lipoid droplets, indistinguishable as such in fixed and stained preparations but represented by vacuoles. This lipoid material imparts a yellowish color to the

*suprarenal cortex of the fresh unstained gland. The narrow zona reticularis has both light and **dark cells**. The dark cells not only stain deeply;*

FIGURE 224 *Human suprarenal gland* The same specimen as Fig. 223, *showing zona reticularis on the left and medulla on the right. Photomicrograph,* 800 ×

they have some brown lipochrome pigment in their cytoplasm. They may be the old cells approaching physiological degeneration. Macrophages are found among the lining cells of the sinusoidal capillaries of the zona reticularis.

The function of the suprarenal cortex is not simple. In fact, this part of the gland has many functions, and more than one active principle is secreted by it. One of its most important functions is regulation of sodium and potassium balance. In cortical deficiency (Addison's disease), great quantities of sodium are excreted by the kidneys, and the blood level of potassium becomes abnormally high. Resistance to stress is greatly impaired. These disturbances are related to inadequate production of several active fractions of cortical secretion.

Other fractions of the suprarenal cortex secretion are related chemically to hormones produced by the gonads. Functionally, little is definitely certain about them.

The storage of vitamin C by the suprarenal cortex is noteworthy. Cholesterol is present in the cortex. The phagocytic activity of macrophages in the zona reticularis has been mentioned.

The relationship of suprarenal cortex to other endocrine glands is important. The anterior lobe of the hypophysis provides a **corticotropic hormone**. The thyroid and gonads can influence suprarenal size and function. The suprarenal glands are relatively much larger at birth than during any other period. They undergo partial involution after birth, losing one-third of their birth weight in the first two weeks, owing to degeneration of the inner part of the cortex, which is of exceptional size.

Medulla of the suprarenal glands: The suprarenal medulla bears little resemblance to the cortex. Its cells are ovoid and are arranged in irregular anastomosing cords (Fig. 224). Among the cords are many wide sinusoids continuous with the capillaries of the cortex and draining into the central suprarenal vein.

Two features characterize the medulla of the suprarenal glands. Its cells exhibit the chromaffin reaction; *i.e.*, they stain a brownish color when fixed in potassium bichromate. They have endings of preganglionic sympathetic neurons among them.

The fine cytoplasmic granules that stain brownish appear to be the precursors of **epinephrine**, the medullary hormone, which is secreted into the venous sinuses. Extracted epinephrine causes vascular smooth-muscle contraction and stimulates massive sympathetic nervous activity when administered hypodermically. The direct innervation of the medullary cells suggests a mechanism for quickly creating such a massive sympathetic response. It is noteworthy that the suprarenal medulla arises embryologically from the same primordia as the sympathetic ganglia. In fact, sympathetic nerve cells are found in the medulla occasionally.

HYPOPHYSIS

The hypophysis, mighty midget among the endocrine organs, is a duplex gland like the suprarenal. Like the suprarenal, one of its portions is of nervous origin and secretes hormones that stimulate motor activity.
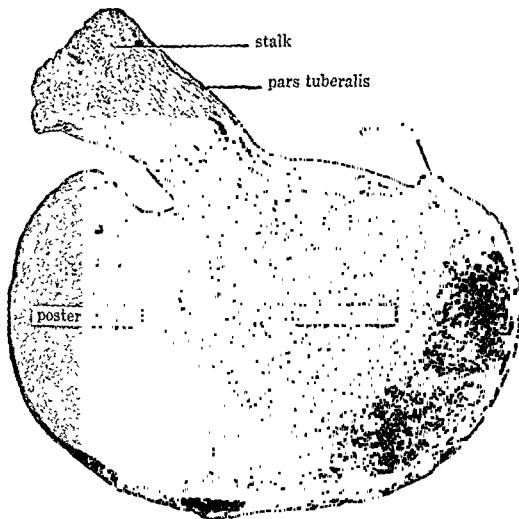
FIGURE 225 Human hypophysis Mid-sagittal section to show its general topography Specimen in the Piersol collection Photomicrograph, 12 ×.

The hypophysis weighs only a little more than half a gram. It lies at the base of the brain in a bony cup lined and roofed over by dura mater. It is encapsulated with dense fibrous connective tissue continuous with the pia mater of the brain. A rich blood supply comes from the arteries at the base of the brain. Veins drain into the cavernous sinus.

The hypophysis may be divided into two parts on an embryological basis One of these, the **pars nervosa**, is still connected with the adult

brain by the **hypophyseal stalk**. The rest of the gland arises from an out-pocketing of the oral ectoderm, known as Rathke's pouch, but no connection remains after the second fetal month.
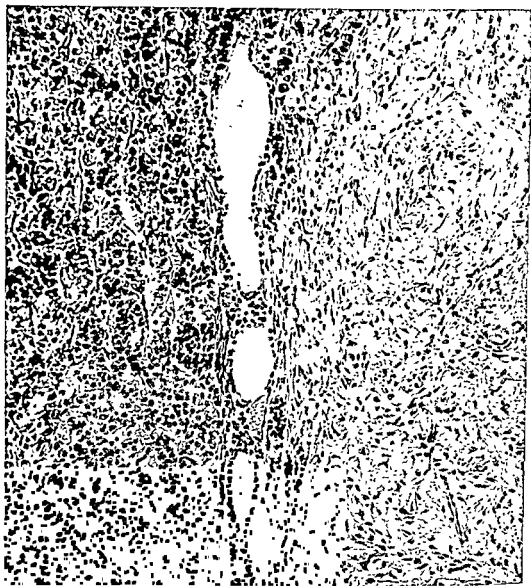
FIGURE 226. Human hypophysis, showing colloid-filled follicles of the pars intermedia in the middle, the pars distalis on the left, and the pars nervosa on the right. Photomicrograph, 150 ×.

Three components are formed by the epithelial diverticulum: the pars intermedia, pars tuberalis, and pars distalis, which is more commonly called anterior lobe. The anterior lobe arises from the anterior wall of the pouch. The pars intermedia develops from the posterior wall and becomes fused with the pars nervosa, the two together constituting the

posterior lobe. The anterior lobe and the neural part of the posterior lobe are the more important components of the hypophysis Relations are shown in Fig. 225.

Anterior lobe: Approximately three-fourths of the gland is comprised
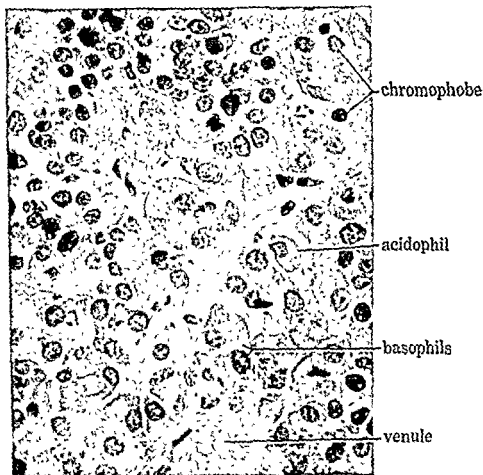
FIGURE 227 Pars distalis of the human hypophysis. Photomicrograph, 600 ×

by the **anterior lobe**, also called **pars distalis**. Its connective-tissue capsule, thicker than that of the posterior lobe, gives rise to fine strands of loose connective tissue, which form the stroma. Collagenous fibers give way to reticular fibers, which support a rich network of capillaries. Some of the capillaries are sinusoidal. Macrophages occur in their walls, just as in the suprarenal gland.

The cells of the anterior lobe are arranged in clumps and cords, intermingling with the sinusoids A few cells form blind acini.

Three types of cells are irregularly distributed throughout the anterior

lobe. The most numerous are **chromophobe cells**, pale and smaller than other types. There is no evidence that these reserve cells secrete. **Acidophil cells**, as the name implies, stain readily with acid dyes, like eosin. It is their cytoplasmic presecretion granules that are acidophilic. Other cells are the **basophils**, only about one-third as numerous as the acidophils. The cells of the anterior lobe are illustrated in Fig. 227.

The **pars tuberalis**, not strictly a part of the anterior lobe, is a thin layer of cells resembling those of the anterior lobe but extending along the hypophyseal stalk onto the brain.

Posterior lobe: A thin region called the **pars intermedia** contains many basophil cells, some of which infiltrate the nervous portion of the **posterior lobe** for a little distance. Nongranular cells line a few follicles that contain colloid. These occupy a well-defined zone between the pars intermedia and the anterior lobe and are shown in Fig. 226.

The **pars nervosa** resembles nervous tissue of the brain but lacks nerve cells. Its cells are related to neuroglia and are called **pituicytes**. Presumably they secrete the hormones of the posterior lobe. *A tract of nerve fibers from the brain passes down the hypophyseal stalk into the neural lobe and ends there.* The formation of the posterior-lobe hormones depends upon the integrity of these fibers. The structure of the pars nervosa is shown in Fig. 226.

Hypophyseal secretions: A remarkable number of hypophyseal hormones have been identified, but little is known about their precise origin. From the neural portion come the substances **pitocin**, which contracts smooth muscle, especially that of the uterus, and **pitressin**, which *raises blood pressure and exerts an antidiuretic effect upon the kidneys.*

The anterior lobe produces, probably in the acidophils, a **growth-promoting hormone**. Excessive secretion in children leads to gigantism and in adults to acromegaly (thickening of the bones). The anterior lobe produces **gonadotropic** hormones, possibly in the basophils. Other hormones are **thyrotropic** and **corticotropic**. Furthermore, a **lactogenic hormone** initiates lactation in the breast at the end of pregnancy. This synopsis only briefly indicates the importance of the master endocrine gland.

OTHER ENDOCRINE ORGANS

The **insular endocrine organ** was described with the exocrine pancreas (page 318). The **ovary, corpus luteum,** and **testis** are important endocrines which can be considered more advantageously with the reproduc-

tive system (pages 375 and 396). Other organs of possible and doubtful endocrine value deserve no more than passing mention.

The **thymus** appears to start on the road toward endocrine structure,
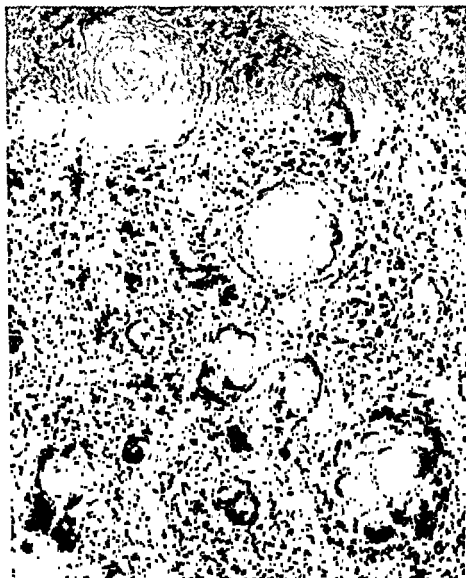
FIGURE 228 Human pineal body showing numerous lobulated and lamellated corpora arenacea Specimen in the Piersol collection Photomicrograph, 150 ×.

but its entodermal components become largely replaced with lymphocytes early in fetal life. We have considered it with lymphatic organs (page 160).

The **paraganglia** are groups of cells resembling those of the suprarenal medulla and are found in the posterior wall of the abdomen at

lobe. The most numerous are **chromophobe cells**, pale and smaller than other types. There is no evidence that these reserve cells secrete. **Acidophil cells**, as the name implies, stain readily with acid dyes, like eosin. It is their cytoplasmic presecretion granules that are acidophilic. Other cells are the **basophils**, only about one-third as numerous as the acidophils. The cells of the anterior lobe are illustrated in Fig. 227.

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Respiratory Organs

The respiratory organs are the lungs and the passages that carry air to and from them. The lungs are highly elastic to permit them to expand and collapse, but the air passages are constructed to remain open and in free communication with the exterior. The lungs are protected in several ways from accidental admission of food and other foreign bodies. The lining of the airways is kept warm by blood vessels, moist by serous secretions, and sticky with mucus. One portion of the airway, the larynx, has become specialized for vocalization. The olfactory organ lies in the upper end of the airway.

NASAL CAVITIES

The nasal cavities are bony and cartilaginous. Each can be divided into three regions on the basis of structural differences in lining membranes: **vestibular, respiratory,** and **olfactory.** The epithelium of each is securely attached to the subjacent bone and cartilage by a lamina propria, poor in elastic fibers and containing numerous small glands.

Vestibular region: The stratified squamous epithelium of the vestibule resembles that of skin but is lightly cornified. This is a transition zone, with hair and sebaceous and sweat glands diminishing toward the respiratory region. Toward the nostrils, the epithelium is thick and has large hairs or vibrissae as well as large sebaceous glands

Respiratory region: The main part of the nasal cavity is lined by a mucous membrane which varies in thickness from several millimeters over the inferior turbinate bone to less than ½mm elsewhere. It is covered with pseudostratified epithelium made up of ciliated columnar cells, with many interspersed goblet cells to secrete mucus. The epithelium rests on a light basement membrane.

various places. They exhibit the chromaffin reaction. Endocrine function is unproved.

The **pineal body**—once considered to be the seat of the soul—may possess an endocrine-like function in regard to sexual development, although this is uncertain. It is a small body invested by pia mater at the back of the roof of the third brain ventricle and in front of the midbrain.

The pineal body of young individuals is formed of fibrous and reticular connective tissue, capillaries, epithelioid cells, neuroglia, and nerve fibers. The most characteristic feature, especially in older individuals, is the presence of brain sand, the *corpora arenacea*, which are laminated and often lobulated concretions of mineral salts. These are illustrated in Fig. 228.

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   The method of microdissection was used for this study. If you wish to read more, look up some of the other references by this author, cited at the end of this article, which have to do with growth in the rabbit's ear chambers.

2. Severinghaus, A. E.: The Cytology of the Pituitary Gland, being Chap. 3, vol. 18, pp. 69–117 in *Publications of the Association for Research in Nervous and Mental Diseases*; Baltimore, The Williams & Wilkins Company, 1938.
   This article with color illustrations will provide a good supplement to your study of the hypophysis. The whole volume is devoted to this gland; see other chapters.

3. Houssay, B. A.: Relations between the Parathyroids, the Hypophysis and the Pancreas, *Harvey Lectures*, Ser. 31, pp. 116–134, 1936.
   You should be familiar with some of the work of this scientist from Argentina, whose studies of endocrines led to a Nobel prize award recently. An English translation of his Fisiologia Humana, by Juan Lewis, will soon be available.

tory tract. The deep layer of the lamina propria blends with the perichondrium or periosteum.

Cilia of the respiratory epithelium are active and serve to move the nasal secretions toward the nasopharynx. The intrinsic glands and one large extrinsic gland, the lacrimal, supply serous fluid to moisten the epithelium and the air that passes over it. Foreign particles, bacteria, and pollen grains are picked out of the air by a film of mucus lying on the epithelial surface.

Olfactory region: The upper part of the nasal cavity is lined by a special olfactory neuroepithelium. This is pseudostratified, about 60 μ thick, lacks cilia, and contains no goblet cells. Besides the usual columnar and basal cells, this epithelium contains nerve cells of a primitive type, the **olfactory neurons**. Each consists of a slender bipolar cell body with a bulging ovoid nucleus, located in the deep portion of the epithelium. The cytoplasm contains neurofibrils. The slender outer process, actually a dendron, passes to the epithelial surface, through which it sends six or eight minute bristle-like projections, the **olfactory hairs**. The inner process, an axon, enters the subjacent lamina propria. Bundles of these **olfactory nerve** fibers pass through the cribriform plate of the ethmoid bone to enter the olfactory bulbs of the brain.

The lamina propria contains small tubulo-acinous **olfactory glands** (Bowman). These are serous, and they open by many rather wide ducts onto the olfactory epithelium, where their watery secretion provides a solvent for air-borne scents. You will recall that a similar mechanism is present in relation to the taste buds on the vallate papillae of the tongue (page 264).

Appendices of the nasal cavity: The maxillary, frontal, sphenoid, and ethmoid bones contain cavities that are lined by thin mucous membranes, continuous with the respiratory mucous membrane of the nose. Tiny apertures of these **paranasal sinuses** permit no significant circulation of air from the nasal passages. Their epithelium is pseudostratified but thinner than that of the nasal cavity. Cilia move secretions toward their apertures indirectly.

A few small mucous glands are found in the lamina propria of the maxillary mucous membrane. Elsewhere the lamina propria is meager and indistinguishable from the periosteum.

Besides the paranasal sinuses, the **nasolacrimal duct** opens into the nasal cavity. This is a tube lined with pseudostratified epithelium and surrounded by a lamina propria containing a venous plexus. Its dilated

The lamina propria is formed of fibrous connective tissue, containing a good many cells, among them lymphocytes and eosinophils. Blood vessels are numerous in the lamina propria. Anastomosing venous channels and capillaries are prominent over the inferior turbinate bone, where
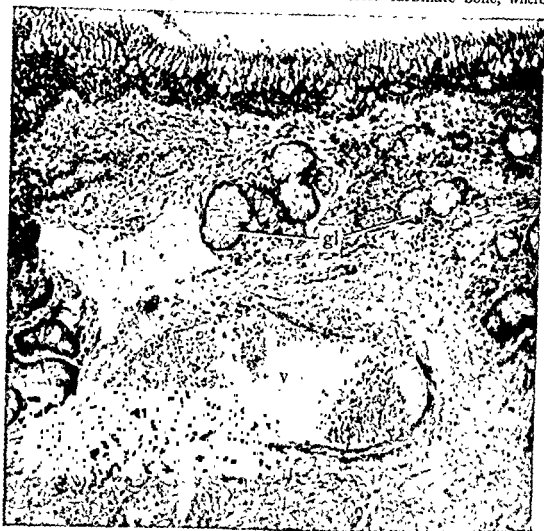
FIGURE 229. Nasal mucous membrane from the inferior turbinate bone of a man. Note the lymphatic, *l*, venule, *v*, and mixed mucous and serous glands, *gl*. The surface epithelium at the top of the figure is pseudostratified and contains many goblet cells. Compare with the tracheal mucosa in Fig. 232. Photomicrograph, 150 ×.

they form **corpora cavernosa**. Engorgement of these cavernous bodies with blood can occlude the airways. The vascular plexus of the lamina propria forms a radiator to warm the air as it passes through the respiratory region of the nose. This region is shown in Fig. 229.

The lamina propria is filled with small tubulo-acinous glands which empty onto the epithelium by numerous ducts. These have mixed serous and mucous acini, as do most glands of this type throughout the respira-
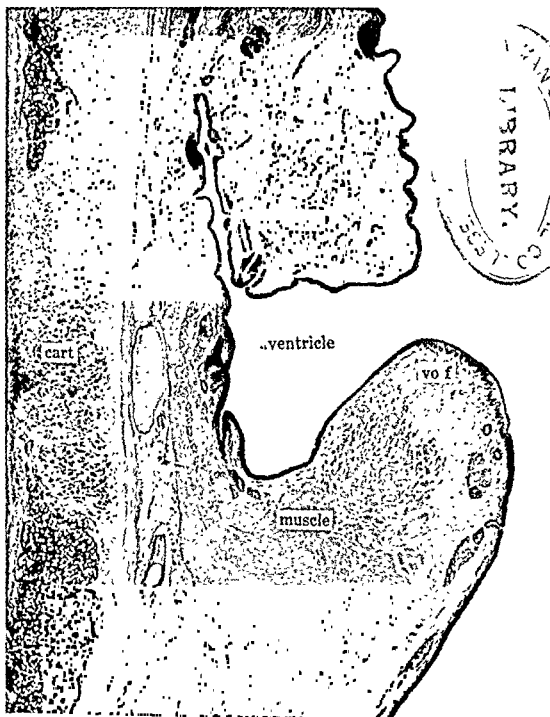
FIGURE 230. Human larynx; frontal section through the partly ossified thyroid cartilage (*cart*) on the left and the laryngeal ventricle with ventricular (*ve f*) and vocal folds (*vo f*) at the upper and lower right. Note the stratified squamous epithelium with papillae of lamina propria on the lip of the vocal fold. Specimen in the Piersol collection Photomicrograph, 13 ×.

upper end, the **lacrimal sac**, receives two small **lacrimal ducts** carrying the tears that have bathed the cornea and conjunctiva of the eye. The lacrimal sac has an epithelium similar to that of the nasolacrimal duct, but the lacrimal ducts are lined with stratified squamous epithelium. The lacrimal gland was considered on page 232.

PHARYNX

The pharynx has been described in relation to the mouth cavity (page 279). The nasal cavities open into the **nasopharynx** at the **posterior nares**. Laterally, the **auditory tubes** (Eustachio) open from the middle ear. The structure of the nasopharyngeal lining is similar to that of the nasal respiratory mucous membrane. A lamina propria contains many lymphocytes; dense lymphatic tissue forms pharyngeal and tubal tonsils. Glands are of the tubulo-acinous mixed type in contrast to the purely mucous glands of the oral pharynx.

There is no sharp line of demarcation between nasal and oral pharynx, nor is the **laryngeal pharynx** clearly bounded. Stratified squamous epithelium of the oral pharynx is continued down to the upper end of the larynx, covering a plate of elastic cartilage, the **epiglottis.** The opening of the larynx, known as the **glottis,** is closed automatically when food is swallowed and when foreign bodies or noxious fumes enter the nose and nasopharynx. It is closed automatically during tensing of the abdomen in straining. It can close voluntarily. Closure is accomplished by sphincter muscles, rather-than by any trap-door action of the epiglottis.

LARYNX

The larynx can be studied to best advantage by dissection. It has a cartilaginous skeleton to which are attached a number of small skeletal muscles, serving as part of the speech mechanism. The mucous membrane of the larynx is mainly of the respiratory type, like that in the nasopharynx. It has pseudostratified epithelium whose cilia move surface secretions toward the pharynx. Glands in the lamina propria are tubulo-acinous and mixed. The lamina propria is well supplied with elastic fibers. Lymphocytes and even lymphatic nodules will be encountered in the laryngeal mucous membrane. A portion of the larynx is shown in Fig. 230.

The mucous membrane has two sets of prominent folds: the **ventricular** and **vocal folds,** or false and true **vocal cords.** Between these folds
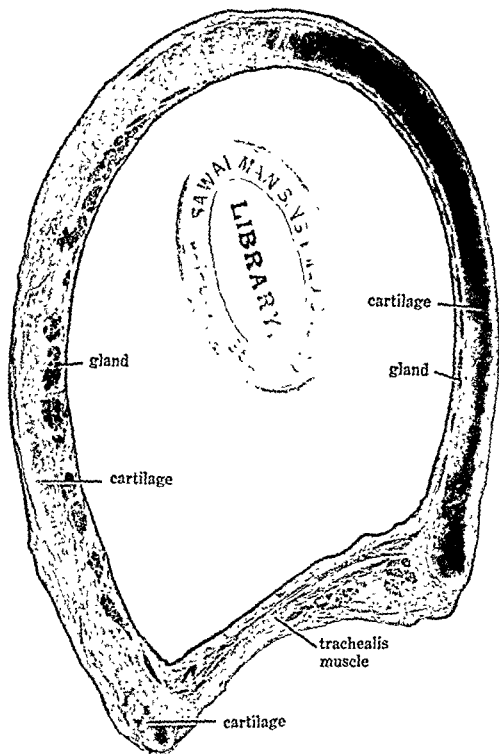
FIGURE 231 Human trachea, sectioned through a cartilage on the right and through the intercartilaginous membrane on the left. Tracheal glands are few and compressed on the right, they are more prominent on the left. Note the trachealis muscle below. Photomicrograph, 6 ×.

is the **laryngeal ventricle**. The true vocal cords have the **vocal ligaments** of elastic fibers in them. Contraction of their skeletal muscle relaxes them. The epithelium over the true vocal cords becomes stratified squamous in consequence of their activity. Few glands are found in them (Fig. 230).

TRACHEA AND BRONCHI

The trachea is a fibrous and cartilaginous tube about 10 to 12 cm. long, extending from the larynx to the bifurcation into the bronchi. One can distinguish a mucous membrane, a submucous layer full of glands, a fibrous and cartilaginous layer, and an adventitia of loose fibrous connective tissue continuous with that of the neck and mediastinum.

Cartilage forms the skeleton of the trachea and gives it a certain amount of rigidity. There are 16 to 20 hyaline **tracheal cartilages** forming incomplete C-shaped rings with openings dorsally, where the esophagus lies. Dense fibrous connective tissue completes this coat by bridging the gaps and becoming continuous with the perichondrium on both sides of the cartilages. It forms a fairly dense membrane at the open ends of the cartilages, where it extends from one cartilage ring to the next. A layer of smooth muscle, the **trachealis muscle**, lies in front of the fibrous membrane connecting the ends of the tracheal rings. These structures are shown in Fig. 231.

The **mucous membrane** of the trachea is similar to that of the larynx and nasopharynx. It is lined with pseudostratified epithelium, which has cilia beating toward the mouth and numerous goblet cells secreting mucous. The epithelium rests upon a well-defined basement membrane. A lamina propria beneath the epithelium has many elastic fibers and contains numerous lymphocytes. Small blood vessels, lymphatics, and nerves course in this layer. Figure 232 shows the mucosa of the human trachea.

The **submucosa** of the trachea is composed of fibrous connective tissue containing the larger vessels and the tracheal glands. These are prominent tubulo-acinous mixed glands (Fig. 232) with many ducts piercing the lamina propria and opening onto the epithelium.

The trachea bifurcates to form two smaller tubes of similar structure. These are the **primary bronchi**. The right bronchus has six or eight cartilaginous rings; the left, nine to twelve. Each primary bronchus enters the hilus of the lung and immediately begins a series of branchings, which culminate in the smallest air passages and the lung alveoli.
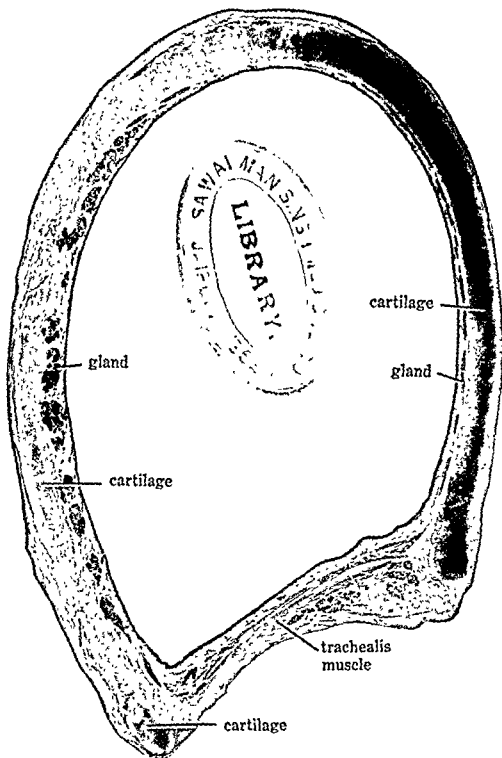
FIGURE 231. Human trachea, sectioned through a cartilage on the right and through the intercartilaginous membrane on the left. Tracheal glands are few and compressed on the right, they are more prominent on the left. Note the trachealis muscle below Photomicrograph, 6 ×.

FIGURE 232. Human tracheal mucous membrane showing ciliated pseudostratified epithelium and mixed glands. Compare with Fig 229. Photomicrograph, 150 ×.

LUNGS

The lung presents an appearance in histological sections which may puzzle you until you realize that it is very much like a large gland in which the acini have been blown up almost to the bursting point. Look-

ing at the lung in this way, you will find a system of ducts, which are the bronchi and their many subdivisions. These are conducting tubes for air. The portions of the lung parenchyma that can be compared with
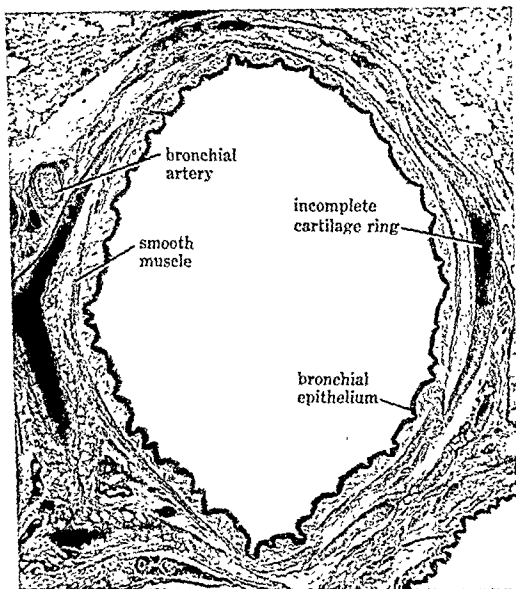
FIGURE 233. Small bronchus in a human lung Photomicrograph, 40 ×.

the secretory ducts and secretory acini of a gland are the respiratory bronchioles, alveolar ducts, and lung alveoli.

Just as a gland is surrounded by a capsule and permeated by trabeculae of fibrous connective tissue transporting its blood vessels, lymphatics, and nerves, so the lung is provided with a similar connective-tissue stroma. The lung capsule is the visceral pleura, and it is covered

with mesothelium. Since the function of the lung is to bring oxygen of the air into close association with the blood, it is evident that the blood supply of the lung is of paramount importance. Furthermore, the lym-
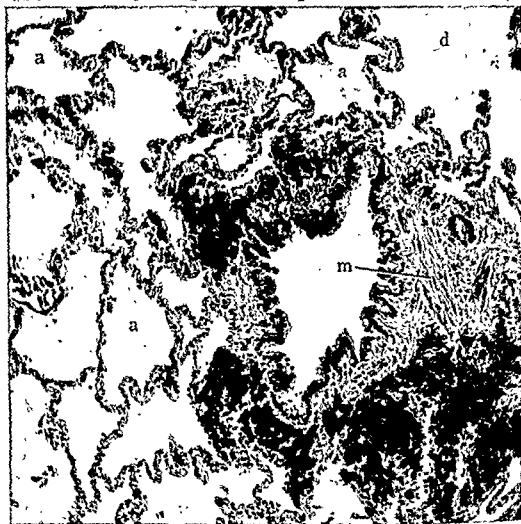
FIGURE 234. Bronchiole in a lung of a city dweller. Note the extensive deposition of carbon pigment in the peribronchial lymphatic tissue. Smooth muscle, *m*, is prominent. Numerous alveoli, *a*, and one alveolar duct, *d*, are shown. Photomicrograph, 150 ×.

phatic drainage of the lung is important because it collects the tissue fluid that is essential in the transfer of gases within the alveolar walls.

The similarity between lung and gland structure is especially striking in the newborn, before the first breath has been drawn At that time, the lung truly resembles an extraordinarily vascular gland. The alveoli are unexpanded and are lined with low simple columnar epithelium which flattens out or ruptures when the lung first expands with air.

Bronchi: Branches of the primary bronchi pass into each lobe of the

lungs from the hilus, accompanied by blood vessels, lymphatics, and nerves. The trabeculae of fibrous connective tissue, in which they course, are rich in elastic fibers. The **secondary bronchi** divide into tertiary
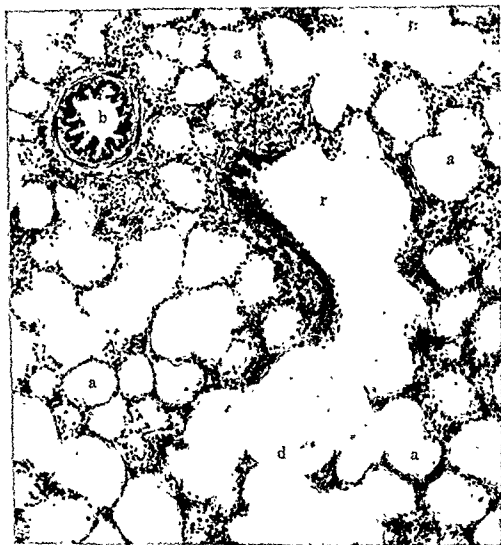
FIGURE 235 Small bronchiole, *b*, respiratory bronchiole, *r*, alveolar duct, *d*, and alveoli, *a*, in the lung of a human infant. Note the ring of smooth muscle in the bronchiole and patches of smooth muscle in the alveolar ducts. Photomicrograph, 150 ×.

bronchi, and so on into smaller and smaller subdivisions through fifty or more generations, as it were. A bronchus of small size is shown in Fig. 233.

As bronchi diminish in size, their epithelium is reduced in thickness until it becomes a simple columnar ciliated lining containing fewer goblet cells. The cilia increase and goblet cells disappear in the smallest

bronchi. The lamina propria, containing lymphocytes, is a thin layer of connective tissue in which reticular and elastic fibers predominate.
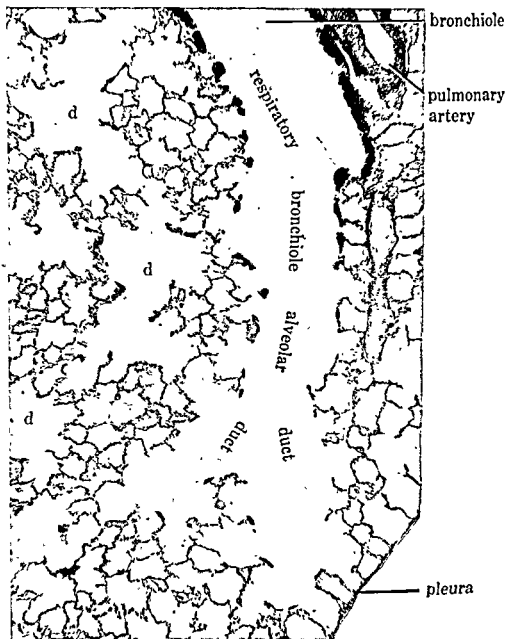
FIGURE 236. Lung of a cat showing continuity of bronchiole, respiratory bronchiole, alveolar duct which branches, and many alveoli. The alveoli are the smallest openings Other alveolar ducts, d, are present. Photomicrograph, 50 ×.

Just beneath the mucosa of the bronchi, there is a layer of smooth muscle. This is not a complete coat but consists of diagonal spirals of muscle running both to the left and to the right and becoming relatively

greater in amount as the bronchi decrease in size. This muscle not only constricts the bronchi but shortens them as it contracts. It plays an im-

large
bronchiole

pulmonary
artery

small
bronchiole

*respiratory
bronchiole
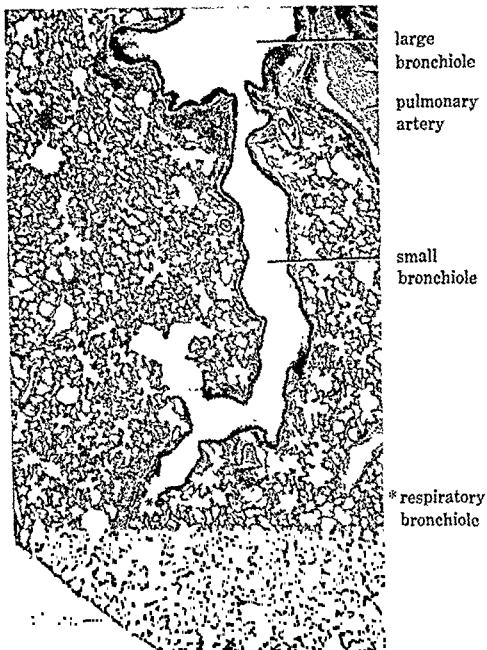
FIGURE 237. Lung of a rat showing continuity similar to that in Fig 236. The bronchiole at the top is the main air duct to this lobe of the lung. Note that the alveoli are very much smaller than those in the cat Specimen by Dr. Harold Koenig. Photomicrograph, 50 ×.

portant part in adjusting the length of the bronchi to contraction and expansion of the lung during breathing.

The cartilaginous C-shaped rings of the main bronchi give way to ir-

regular and incompletely encircling plates of cartilage in the lesser bronchi. In the larger bronchial branches, no posterior defect, like that in the trachea and primary bronchi, is produced by the cartilages. The cartilaginous plates disappear altogether in the smallest bronchi, which are only about 1 mm. in diameter.

The bronchial glands are mixed, like those in the trachea. They lie outside the smooth muscle and are found in the smallest bronchi, sometimes extending a little farther peripherally along the respiratory tree than the cartilaginous plates.

Bronchioles: When the passages become less than 1 mm. in diameter, they are called **bronchioles**. These little conducting tubes are lined with simple columnar ciliated epithelium, becoming partly nonciliated distally. They have no goblet cells, no glands, and no cartilaginous plates. They have relatively much smooth muscle which can constrict and shorten them. They mount guard over the delicate respiratory portions of the lung. Their surrounding stroma is continuous with that of adjacent lung alveoli. Elastic tissue is abundant in the larger bronchioles, one of which is shown in Fig. 234.

Respiratory bronchioles: Terminal bronchioles are lined with low simple columnar epithelium, mostly lacking cilia. They have diagonal bands of smooth muscle forming an incomplete layer in their walls, as it does in the larger bronchioles. This fenestration leaves regions in which the walls of these small tubes are unusually thin. Such tubes are designated **respiratory bronchioles**. The reason for this is that their extremely thin walls become bubbled out into air sacs between the crisscrossing bands of smooth muscle. These air sacs are exactly like the terminal lung alveoli. A respiratory bronchiole will be seen in Fig. 235.

Alveolar ducts: As you follow respiratory bronchioles peripherally, you will find that each one branches into several very incompletely circumscribed **alveolar ducts**. These are clearly depicted in Figs. 236 and 237. The walls of these channels are even more extensively ballooned out into air sacs than those of the respiratory bronchioles. Their interlacing diagonal bands of smooth muscle appear in sections as little knots of tissue. Each alveolar duct may have several branches.

Alveoli: The terminal subdivisions of the respiratory tract are the **alveoli**, or air sacs. They begin as outpocketings of the respiratory bronchioles but are especially prominent around the alveolar ducts. As you study them in histological sections, remember that in life they are even more dilated than you see them. Removal of a lung and its fixation results in

partial contraction, owing to the richness of elastic fibers in its stroma (Fig. 238).

Alveoli have an exceedingly thin epithelial lining.[1] This forms the simplest possible barrier between the film of intraalveolar fluid and the tissue fluid surrounding the capillaries in the alveolar walls. This rich capillary plexus should be studied in injected specimens cut into thick sections and placed under a binocular microscope set to produce a stereoscopic effect. The capillaries occupy a minute amount of stroma con-
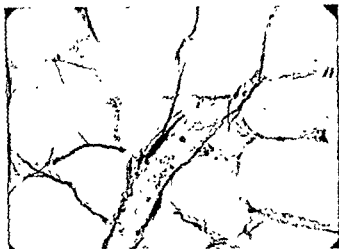
FIGURE 238. Elastic fibers in the finest subdivisions of the pulmonary stroma, thick section Photomicrograph, 300 ×.

sisting mainly of reticular and elastic fibers. Macrophages are commonly observed within the alveoli (Fig. 47C). Small apertures in alveolar walls provide a few intercommunications between alveoli.

There are no lymphatic capillaries in the walls of lung alveoli, but lymphatics do course in the stroma around the bronchioles. Tissue fluid in the delicate stroma between the alveolar epithelium and capillary endothelium diffuses back to the trabecular lymphatic vessels, just as it does in the cords of cells in the liver.

Blood vessels, lymphatics, and nerves· Blood of low oxygen content is brought to the lungs by the **pulmonary arteries** for aeration. Branches accompany the bronchial tree. The finest pulmonary arterioles convey their blood to the rich alveolar plexuses beginning at the level of alveo-

[1] Some believe that the expansion of the lung at birth ruptures *the low columnar epithelium of the alveoli* and that henceforth there is no epithelium lining these air sacs This view is not generally held It would place the air in direct contact with the tissue fluid.

regular and incompletely encircling plates of cartilage in the lesser bronchi. In the larger bronchial branches, no posterior defect, like that in the trachea and primary bronchi, is produced by the cartilages. The cartilaginous plates disappear altogether in the smallest bronchi, which are only about 1 mm. in diameter.

The bronchial glands are mixed, like those in the trachea. They lie outside the smooth muscle and are found in the smallest bronchi, sometimes extending a little farther peripherally along the respiratory tree than the cartilaginous plates.

Bronchioles: When the passages become less than 1 mm. in diameter, they are called **bronchioles**. These little conducting tubes are lined with simple columnar ciliated epithelium, becoming partly nonciliated distally. They have no goblet cells, no glands, and no cartilaginous plates. They have relatively much smooth muscle which can constrict and shorten them. They mount guard over the delicate respiratory portions of the lung. Their surrounding stroma is continuous with that of adjacent lung alveoli. Elastic tissue is abundant in the larger bronchioles, one of which is shown in Fig. 234.

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Another system of arteries enters the lungs. These are the **bronchial arteries** that come from the aorta. They supply the bronchi and the pleura with oxygenated blood. The blood carried by them may return by way of bronchial veins or may join that of the pulmonary veins.

Lymphatic vessels of the lung form two plexuses. Those which course through the pleura form a superficial plexus. A deep plexus follows the course of the bronchial tree. There are a few communications between these two plexuses. Lymph nodes occur in the root of the lung. The afferent lymphatic vessels of these nodes come from both lymphatic plexuses. The efferent vessels from the lymph nodes enter the mediastinum.

Nerves course along the bronchial tree from the pulmonary plexus in the root of the lung. They are concerned mainly with motor innervation of the blood vessels and the bronchial musculature, but sensory nerve fibers also are present.

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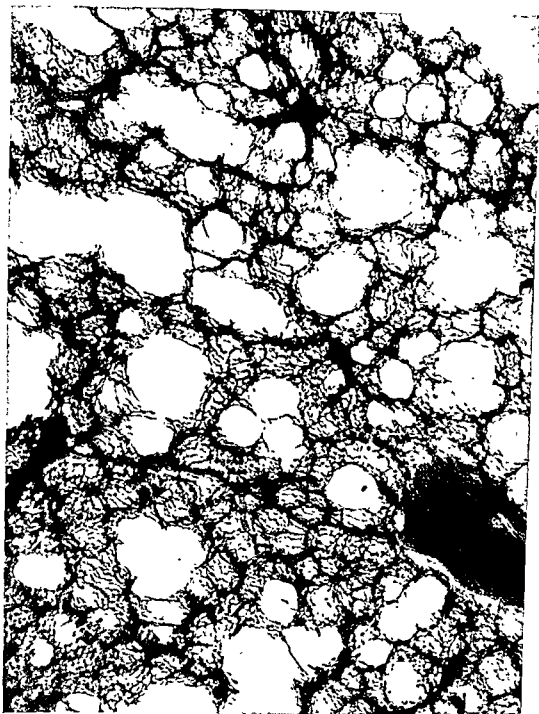
FIGURE 239. Pulmonary capillary plexuses among alveoli in the lung of a European hedgehog injected through the pulmonary artery. Specimen in the Piersol collection, but may have belonged to Joseph Leidy. Photomicrograph, 80 ×.

lar ducts. **Pulmonary veins** take oxygenated blood back to the heart. Their tributaries do not accompany the bronchial tree. They reach the root of the lung but course independently in the pulmonary stroma.

with the dense fibrous connective tissue that invests the calyces and pelvis. It lines the renal sinus and continues out of the hilus over the external renal surface as the **capsule** of the kidney (Fig. 241). As blood
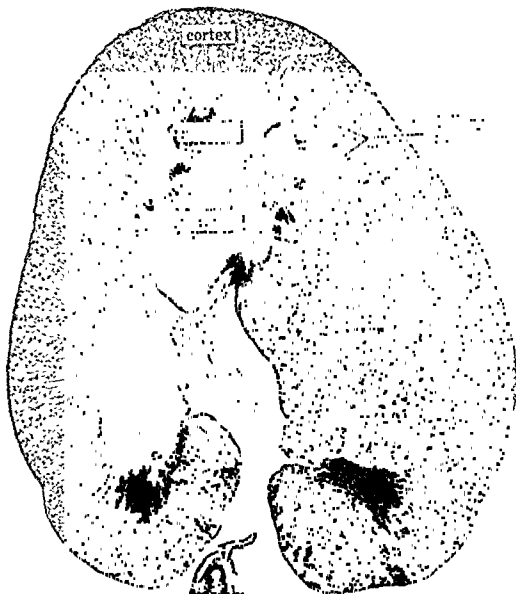
FIGURE 240. Kidney of a human infant, cut in cross section. Most of the contents of the renal sinus have been removed, leaving only parts of two calyces. Photomicrograph, 6 ×.

vessels, lymphatics, and nerves pierce the wall of the renal sinus to enter the kidney, they are accompanied by small amounts of connective tissue, which permeates the entire organ to form the renal stroma.

The **renal stroma** is less conspicuous than is that of glands. No septa nor trabeculae divide the kidney into lobes and lobules. The finest sub-

Excretory Organs

The excretory organs comprise the kidneys, ureters, urinary bladder, and urethra. The kidneys are of major importance. The rest of the excretory organs are simply conducting and storage mechanisms.

KIDNEYS

You learned in botany that beans are kidney-shaped. Anatomists tell you that the kidneys are bean-shaped. We are less concerned about their shape than how they work. Much can be learned about the function of the kidney from a study of its intrinsic structure. There is no other organ a knowledge of whose blood supply is more important.

A good way to begin a study of the kidney is to look at a frontal section cut through the center of the whole organ. If a human kidney is unobtainable, get one from an animal, but bear in mind that there are species differences. You will see a good deal of fat and areolar tissue filling a space in the center on the hilus side. This space, the **renal sinus**, is occupied by the **renal pelvis** and major and minor **calyces** as well as by branches of the renal blood vessels. Figure 240 shows a cross section through an infant's kidney.

The kidneys have the structure of glands, but they produce no exocrine secretion. How they form acid urine from an alkaline filtrate of blood plasm, you will study in detail in courses in physiology. Kidneys resemble compound tubular glands, each with eight or more lobes not clearly circumscribed. The functional elements of the kidneys are called nephrons. A system of excretory ducts carries off the urine and empties it into the calyces of the renal pelvis.

General architecture. The areolar tissue of the renal pelvis blends

striated. The papillae and pyramids comprise the **medulla** of the kidney. The base of a pyramid is directed toward the surface of the kidney, and it is not sharply demarcated because stripes of medullary substance go beyond the medulla into the **cortex** of the kidney, forming **medullary**
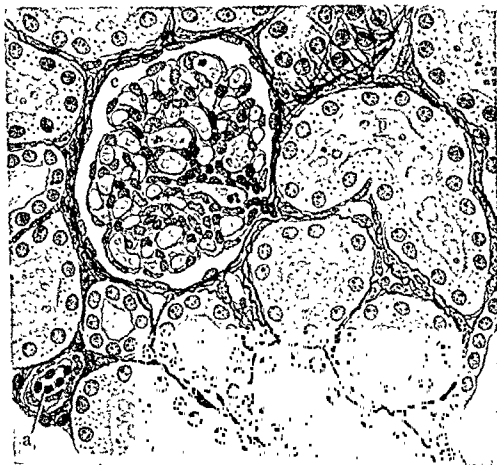
FIGURE 242. Renal corpuscle and tubules of a human kidney. The glomerulus is sectioned near its vascular pole; *a*, arteriole; *c*, renal capsule; *d*, distal convoluted tubule, *p*, proximal convoluted tubule. Reticular fibers of the renal stroma are stained by the silver carbonate method. 300 ×.

rays. In a gross section you will see that each pyramid is surrounded, except at its papilla, by cortex of the kidney (Fig. 240).

Between pyramids, the cortex reaches the surface of the renal sinus, forming interpyramidal **renal columns.** These are not actually columns but regions of cortical substance surrounding the cones of medullary substance. Medullary rays and pyramids contain straight portions of the renal tubules and the collecting tubules, whereas the cortical substance contains convoluted tubules and renal corpuscles. You will need microscopical preparations to see these structures.

divisions of the stroma become reticular (Fig. 242). Delicate basement membranes are formed beneath the tubular epithelium. These are especially well shown in Fig. 246.

FIGURE 241 Human kidney, showing connective-tissue capsule (above) and cortex containing convoluted tubules, renal corpuscles, and blood vessels; medullary rays begin in the lower part of this region Photomicrograph, 80 ×.

At birth, lobes of the kidney are clearly indicated by surface markings. Later the lobes fuse completely. Indication of lobulation in the adult is seen in the multiple projections of renal medullary substance into the renal sinus. These are the conical **renal papillae,** each one clasped by a minor calyx, into the lumen of which urine is emptied from openings of 10 to 20 ducts.

Renal papillae form the apices of **renal pyramids** which grossly appear
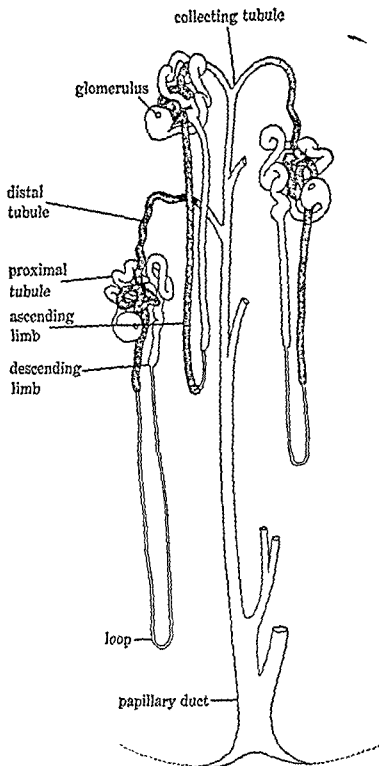
FIGURE 244. Diagram of three nephrons and their collecting tubule. Distal tubules are stippled, other parts of the nephron are unshaded. Redrawn after G. C. Huber, from J. L. Bremer and H. L. Weatherford, *A Textbook of Histology*; Blakiston, 1944.

The nephron: The part of the **uriniferous tubule** that forms the urine and corresponds to the secretory portion of a true gland is called the **nephron**. This, the functional unit of the kidney, consists of a capsular portion and a tubular portion. The tubular part of the nephron is sub-
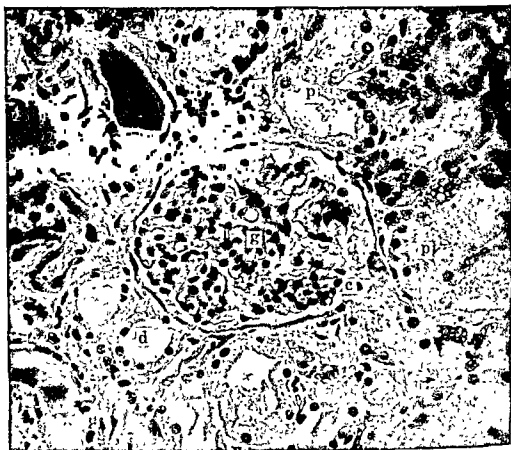
FIGURE 243. Renal corpuscle and tubules of a human kidney. The glomerulus is sectioned through its tubular pole, *c*, where the renal capsule joins a proximal convoluted tubule, *d*, distal convoluted tubule, *g*, glomerulus; *p*, proximal convoluted tubule Photomicrograph, 300 ×.

divided further into proximal and distal segments, formed by simple columnar epithelium, connected by a short length of thin tubing of simple squamous epithelium (diagrammatically represented in Fig. 244).

The **renal capsule** (Bowman) is a sac of simple squamous epithelium invaginated by a tuft of arterial capillaries, the **glomerulus.** The two together form the **renal corpuscle** (Malpighi), a small body about 0.2 mm. in diameter. The capsule has a wall of columnar cells in the fetus, but these cells become flattened after birth when the kidney suddenly takes over the excretory function of the placenta. You will have to look

FIGURE 245. Brush border on the cells of two human proximal convoluted tubules. A distal tubule (smaller) lies between them near the top of the figure; a small part of a renal corpuscle is at the bottom of the figure. Specimen from Prof. S. I Kornhauser; Quad stain. Photomicrograph, 1200 ×.

carefully to see the thin lining of the adult capsule and its reflection onto the capillary tufts of the glomerulus (Figs. 242 and 243).

Each renal corpuscle has a vascular pole at which an afferent arteriole enters and an efferent arteriole leaves (Fig. 242), and a tubular pole where the lumen of the capsule opens into the proximal tubule (Fig. 243). Since each renal corpuscle measures about 200 μ in diameter, you will have to examine a number of them in thin sections to find these poles.

The **renal tubule,** which arises at the capsule, first pursues a tortuous course in the renal cortex near the capsule, then forms a long straight loop into the medullary rays and pyramids. Returning to the cortex, it engages in another smaller series of convolutions before joining an excretory collecting tubule. Thus, three parts are distinguishable on the basis of the course of the tubular portion of the nephron: **proximal convoluted** and **distal convoluted** tubules and the **loop** (Henle).

From the standpoint of minute structure and function, the proximal convoluted tubule and the thick part of the descending straight limb of the loop are alike. The thick straight ascending limb of the loop and the distal convoluted tubules are alike. The thin portion of the loop has a structure significantly different from either.

The **proximal convoluted tubule** is long and tortuous. Since it measures about 14 mm. in length, or one-half the length of the entire nephron, and since it makes many turns, you may expect to encounter sections of it in many places in the vicinity of one renal corpuscle. The straight portion of the proximal tubule passes into a medullary ray to begin the descending limb of the loop and is spoken of as the **medullary segment.**

The proximal tubule is thickest of all parts of the nephron. It has wide low columnar cells resting on a basement membrane. They are basally striated and possess a brush border on their free surface, indicating their absorptive function (Fig. 245). Cells do not have distinct boundaries where one joins another.

The **thin segment** of the nephron continues the downward course of the medullary segment of the proximal tubule and is of variable extent. When associated with a renal corpuscle located in the outer part of the cortex of the kidney, it is short. Nephrons whose corpuscles lie near the base of a pyramid have long thin segments which may extend almost to the apex of the pyramid and then pass for some distance back up the ascending limb of the loop. Observe cross sections of these in Fig. 246.

Cells of the thin segment are squamous but not so flat as the endo-

tubules, they are cut into fewer sections. You will find one or two near the vascular pole of the renal corpuscle (Figs. 242 and 243). One convolution always makes contact with the thick-walled afferent arteriole of the glomerulus. There it displays taller, thinner columnar cells at the point of contact.

Collecting tubules: The distal convoluted tubule terminates in a duct, the **collecting tubule.** There is an arched portion in the cortex, but this is short and joins the straight collecting tubule which passes through a medullary ray into a pyramid. In the pyramid, it joins other straight collecting tubules. They increase in size from about 40 to 200 μ before emptying at the papilla into a minor calyx. The largest are called **papillary ducts.**

The cells lining the collecting tubules form a clear low columnar epithelium, which resembles that of excretory ducts of glands. Cell boundaries are distinct. As the ducts increase in diameter, the cells increase in height. They become tall simple columnar cells in the largest, papillary ducts (Fig. 246).

Renal blood vessels: Branches of the **renal artery** pass from the renal sinus into the cortical substance between renal papillae. When each of these arteries reaches the level of the base of the pyramid, it terminates in a number of short arching branches that run parallel to the kidney surface. These are the **arcuate arteries,** which do not anastomose with one another. They branch into **interlobular arteries** of the cortex. These leave the arcuates at right angles and ascend toward the surface, one lying between each two medullary rays, as a rule.

The interlobular arteries are tree-like. From the central trunk arise numerous side branches, the **afferent glomerular arterioles,** which enter the vascular poles of the renal corpuscles. The system of arcuate and interlobular arteries is so complete that no afferent arteriole needs to course very far to reach its renal corpuscle (Fig. 247).

The afferent glomerular arterioles divide into four or five branches at the vascular pole, and each of these again divides. A series of intertwining, although separate and nonanastomosing, capillary loops builds the glomerulus. The capillaries recombine to form, not a venule, as you might expect, but another arteriole, the **efferent glomerular arteriole.** The efferent arteriole has a smaller caliber than the afferent arteriole.

As the afferent arteriole approaches the glomerulus, its wall is thickened. Its smooth-muscle cells take on a clear swollen nonfibrillar appearance and look like epithelial cells. This thick-walled part of the vessel

thelial cells of adjacent capillaries. Furthermore, the absence of blood in
the lumen of the thin segments helps you distinguish them from capil-
laries.

The distal tubule begins at the **thick segment** of the loop. Its course
is in a pyramid and a medullary ray as it passes back to the vicinity of its
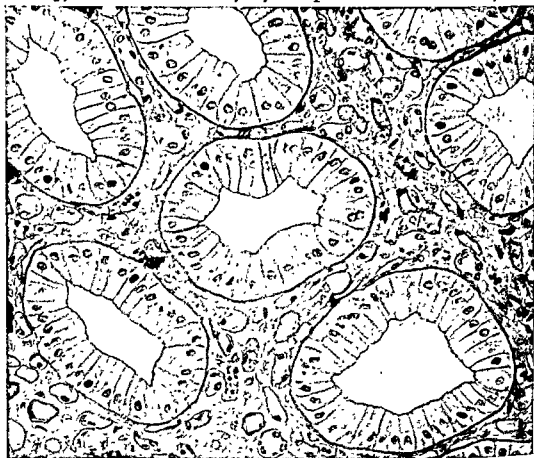
FIGURE 246 Inner zone of the medulla of a rabbit kidney sectioned across a renal
papilla and stained with iron hematoxylin. Large ducts are collecting tubules, small
ducts are thin limbs of nephron loops and blood capillaries, some of the latter identi-
fied by dark-stained red corpuscles inside Specimen by the late Dr. George de Renyi
Photomicrograph, 600 ×.

own renal corpuscle. There, in the cortex, it becomes the **distal convo-
luted tubule.**

Cells of the distal tubule are low columnar, smaller and narrower
than those of the proximal tubule. They, too, rest on a delicate basement
membrane. Their nuclei appear closer together than do the nuclei of the
wide cells of the proximal tubule. The cytoplasm stains lightly and is
not distinctly striated. There is no brush border. Since the distal con-
voluted tubules are considerably shorter than the proximal convoluted

resembles the blood vessels in the carotid body (page 151). The name **juxtaglomerular apparatus** has been given to it, and an endocrine function has been suggested.

As soon as the efferent arteriole leaves the glomerulus, it breaks up into another series of capillaries, which are extremely numerous. They form rich networks around all the renal tubules in the cortex and medullary rays. A delicate reticular stroma supports this capillary bed.

The renal pyramids are supplied by capillary networks which arise from branches of the efferent arterioles of the glomeruli nearest the medulla. They form capillary networks about the tubular loops and are less tortuous than those of the cortical substance. All parts of the renal tubule are supplied by blood that has already traversed the filtration units, *i.e.*, the renal glomeruli. Capillary blood pressure is low.

Tributaries of the **renal veins** course with interlobular and arcuate arteries and bear the same names. Their tributaries, in turn, are venules, which drain blood from the tortuous capillaries of the cortex. Straight venules receive blood from the medulla. They enter the arcuate veins directly.

Renal function: The kidney is the most important organ for the maintenance of constant composition and volume of the body fluids. It takes enormous quantities of water out of the blood plasma, but it puts most of this back. Water serves as the vehicle for dissolved substances, many of which are selectively excreted in the nephrons. Filtration takes place in the 2 to 8 million renal corpuscles; 160 to 190 l. of filtrate are removed from the blood daily. This fluid has all the constituents of blood plasma except fat and large protein molecules. The efferent glomerular arteriole helps regulate the pressure of blood in the glomerulus. This pressure must be high enough to offset the pressure of fluid in the capsule plus the osmotic pressure of the blood plasma proteins. If the efferent arteriole were as large or larger than the afferent arteriole, filtration pressure might be too low to permit urine formation.

The tubules put water and many of the solutes back into the blood by selective absorption. The higher pressure inside the tubules and the much lower capillary blood pressure should be borne in mind. The glomerular filtrate enters the proximal tubule, whose cells with their brush border have a structure suggestive of their absorptive function Glucose is completely returned to the blood under normal conditions. Amino acids are likewise removed from the filtrate. Urea and some electrolytes are partly absorbed.
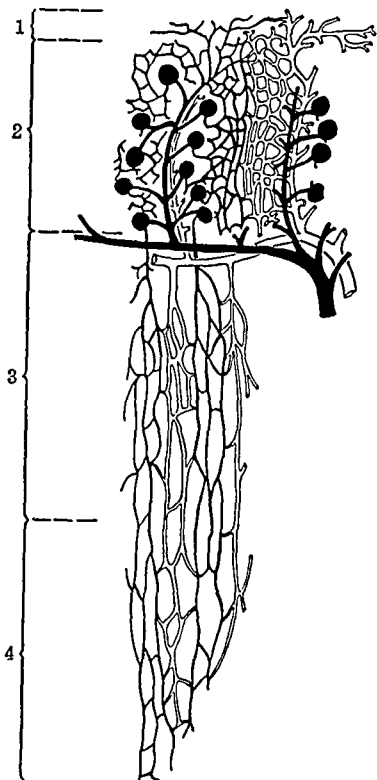
FIGURE 247. Diagram of the kidney cortex and medulla. Arteries and capillaries on arterial side are black, veins and capillaries on venous side are white. Numerals refer to 1, fibrous capsule, 2, cortex, 3, outer zone of medulla, 4, inner zone of medulla. Redrawn from A. A. Maximow and W. Bloom, *A Textbook of Histology*, Saunders, 1944.
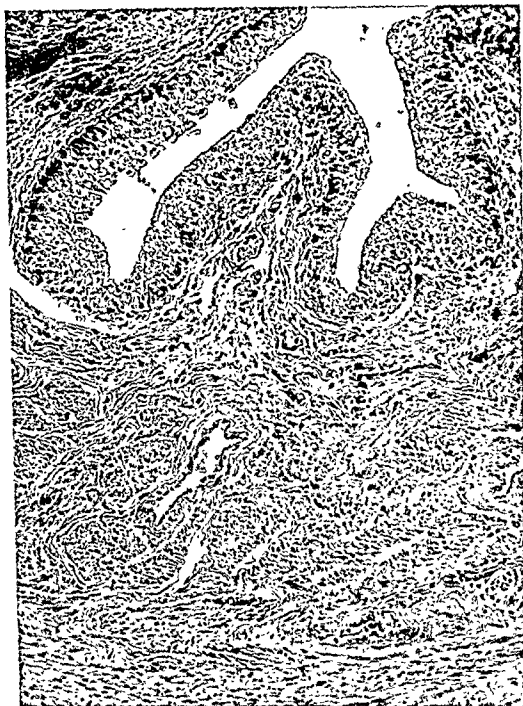
FIGURE 249. Portion of the human ureter Note the inner longitudinal muscle bundles, the outer circular muscle is seen at the bottom of the figure. Compare with illustrations of genital ducts Photomicrograph, 150 ×.

tubules. A disturbance of the pancreatic insular gland (diabetes mellitus) produces a condition in which the nephrons are overloaded with sugar.

Water is absorbed in great quantities, both proximal and distal tubules being engaged in this activity. Water absorption is a major function of the distal tubule, even though its cells lack a brush border. The role of the tubules in regulating the acid-base balance will be considered in physiology.
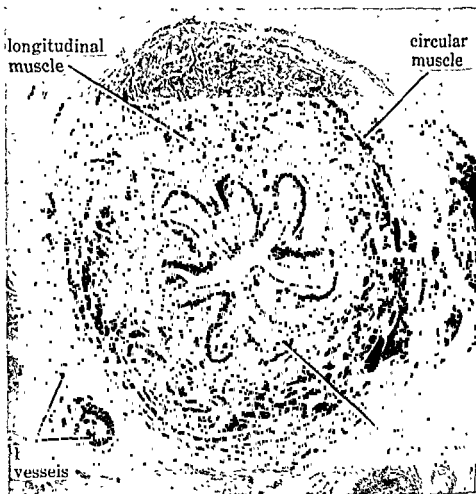
FIGURE 248. Human ureter. Photomicrograph, 40 ×.

A substance that can increase local blood pressure is produced by combination of **renin**, arising in the kidney, with a protein fraction of the blood. The juxtaglomerular apparatus has been suggested as a possible site of secretion of renin.

Control of renal function by the endocrine organs should be recalled. Deficiency of secretion of the posterior lobe of the hypophysis leads to greatly increased water output (diabetes insipidus) and a compensatory thirst. Deficiency of suprarenal cortical secretion results in decreased absorption of sodium and increased absorption of potassium ions in the
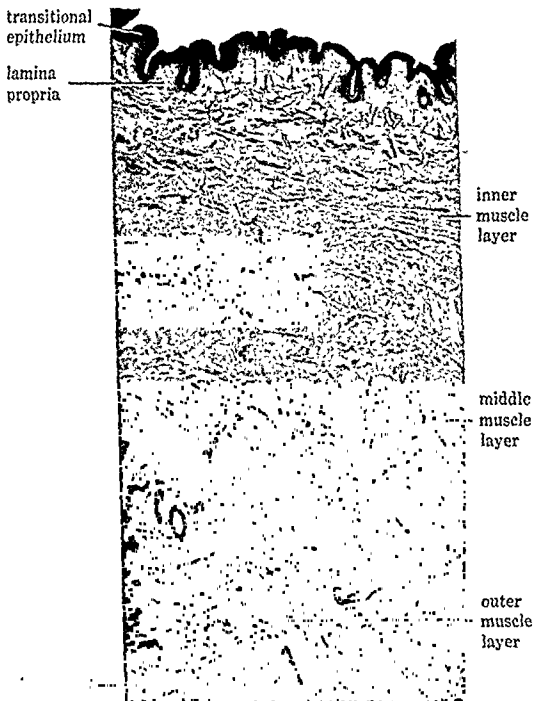
FIGURE 250 Urinary bladder of a pig; contracted state Compare with Fig. 28. Photomicrograph, 20 ×.

many elastic fibers and small blood vessels. It, too, is capable of accommodation to changing conditions in the bladder.

The **muscularis** has three layers. The inner and outer lie in the same

RENAL DUCTS

The duct of the kidney is formed by the ureter and its expanded proximal end, the renal pelvis. Extensions of the pelvis are the calyces that clasp the papillae. The two ureters terminate by passing diagonally through the wall of the urinary bladder. The walls of the several parts of the renal duct are similar in structure, consisting of mucosa, muscularis, and adventitia.

The **mucous membrane** is lined with transitional epithelium, several cells thick and lacking a basement membrane. The lamina propria beneath this merges directly with the fibrous connective tissue among the bundles of smooth muscle of the middle coat. It contains no glands. There is no submucosa. In the ureter, the mucous membrane is thrown into longitudinal folds, which impart a stellate appearance to its lining in cross sections (Figs. 248 and 249).

The **muscular coat** consists of inner longitudinal and outer circular layers, which is just the opposite of that in the muscularis of the digestive organs. Near the bladder, an accessory outer longitudinal layer is added. In the calyces, the circular muscle is thick. Both layers are well developed in the renal pelvis, but the longitudinal layer consists only of scattered bundles throughout most of the ureter. The muscularis of the renal calyces and pelvis undergoes peristaltic contractions which squeeze the urine on into the ureters. The well-developed longitudinal layer at the lower end of the ureter tends to maintain the integrity of the ureteral orifice into the bladder.

The **adventitia** of the ureter consists of fibrous connective tissue containing blood vessels, lymphatics, and nerves. A considerable quantity of fat is found around it in the renal sinus.

URINARY BLADDER

Although the urinary bladder has a structure much like the ureter, its wall is thicker, mainly because of an increase in smooth muscle. Its appearance varies with the degree of distention (Fig. 250).

The **mucous membrane** of the empty bladder is thrown into heavy folds. The epithelium is transitional and may be six or eight cells thick. When greatly distended, the bladder has only two or three layers of cells in its epithelium, and the surface cells are very much flattened (Fig. 28). The lamina propria of the mucous membrane is quite loose and contains

The structure of the **male urethra** differs considerably from that of the female because it is incorporated into the penis. Its glands have under-

FIGURE 251. Human female urethra (below) and anterior wall of the vagina (above), sectioned at the level of the urogenital diaphragm, connective-tissue stain. The adventitia of the vagina and urethra join at 1, the inner longitudinal and outer circular smooth-muscle layers are shown at 2 and 3, the sphincter of skeletal muscle is seen, darkly stained, at 4. Photomicrograph, 10 ×.

gone extensive development, and it has become an important genital passage. Consequently it will be described in the next chapter (page 389).

plane. The middle layer is thickest, and its fibers run at right angles to the inner and outer layers. There is much loose fibrous connective tissue permeating muscle bundles, and this permits them to shift during distention and collapse of the bladder. An **internal urinary sphincter** muscle is provided at the place where the urethra begins.

The **adventitia,** or outer coat of the bladder, contains the larger blood vessels, lymphatics, and nerves. It is covered by mesothelium of the peritoneum over part of the bladder.

URETHRA

The urethra is a duct connecting the lower end of the bladder with the exterior and is much shorter in the female than in the male, measuring only about 3 or 4 cm. in length. The female urethra presents a structure of no great complexity. It is illustrated in Fig. 251.

The **mucous membrane,** like that of other large ducts emptying onto the body surface, has an epithelium that changes to stratified squamous near its orifice. Stratified columnar or pseudostratified epithelium may be present just before the stratified squamous epithelium begins. Elsewhere the epithelium is like that of the bladder. It is the transitional type.

The mucous membrane is folded longitudinally, and there is an especially prominent fold posteriorly. A few small **urethral glands** of tubuloacinous type secrete mucus. Some of them empty into little epithelial pockets. Two small groups of them inconstantly open directly onto the vestibule by means of ducts on either side of the urethral orifice instead of into the urethra. These are the **paraurethral ducts.** All the glands of the female urethra are homologous with those of the prostate in the male.

The lamina propria of the female urethra is loose and resembles that of the bladder, with which it is continuous. It does not form a true corpus spongiosum.

The **muscularis** of the urethra is formed by prominent inner longitudinal and outer circular layers, which are separated by a venous plexus. The circular muscle enters into the formation of an internal sphincter at the junction of the urethra with the bladder. An external sphincter made of skeletal muscle is present at the lower end of the urethra, as shown in Fig. 251.

In the **adventitia** are blood vessels, lymphatics, and nerves. These course in fibrous connective tissue, which blends with that of the surrounding perineum.

The structure of the **male urethra** differs considerably from that of the female because it is incorporated into the penis. Its glands have under-

FIGURE 251. Human female urethra (below) and anterior wall of the vagina (above), sectioned at the level of the urogenital diaphragm, connective-tissue stain. The adventitia of the vagina and urethra join at 1; the inner longitudinal and outer circular smooth-muscle layers are shown at 2 and 3, the sphincter of skeletal muscle is seen, darkly stained, at 4 Photomicrograph, 10 ×

gone extensive development, and it has become an important genital passage. Consequently it will be described in the next chapter (page 389).

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2. Huber, G. C.: Renal Tubules, being Chap. 24, vol. 2, pp. 935–977, in *Special Cytology*, 2d ed., E. V. Cowdry, editor; New York, Paul B. Hoeber, Inc., 1932.
   A phylogenetic study of the structure of nephrons forms the basis for this account. The methods of wax plate reconstruction and of maceration and teasing were used by Prof. Huber for his own investigations.

Male Reproductory Organs

The reproductory organs of the male are those concerned with sperm formation (the testis); with sperm transportation (the epididymis, spermatic ducts, and urethra), with secretion of a suitable fluid vehicle for sperm (the seminal vesicles, prostate, and bulbourethral glands); and with copulation (the penis). The endocrine function of the testis is as important as spermatogenesis; groups of interstitial cells are provided for this purpose.

TESTIS

General structure: The testis has the structure of a compound tubular gland with about 250 lobules. It has a remarkably heavy capsule of dense fibrous connective tissue, called the **tunica albuginea**, the deep layer of which is vascular (Fig. 253). The testis lies in the scrotum in a small peritoneal sac called the **tunica vaginalis**, which has become separated from the abdominal cavity during development.

At the hilus, which is called the **mediastinum testis**, the dense fibrous connective tissue is thickened. Septa pass through the testis from hilus to capsule and incompletely subdivide the organ into lobules. Within each lobule, the fibrous connective tissue forms an abundant stroma around the **seminiferous tubules**, carrying blood vessels, lymphatics, and nerves and containing endocrine **interstitial cells**.

A lobule of the testis contains from one to three extensively **convoluted tubules**, each of which may be as long as 70 cm. These form loops. Branches and anastomoses occur in some of the loops. The two ends of each loop join a **straight tubule** in the mediastinum, and the straight tubules join a network of thin irregular channels, called the **rete testis**,

likewise in the mediastinum. These empty by about a dozen efferent ductules into the head of the epididymis.

The efferent ductules and the epididymis are extraordinarily convoluted tubules over the upper pole of the testis. Toward the lower pole, convolutions diminish and the epididymis joins the ductus deferens which enters the spermatic cord to pass into the abdomen. The ductus deferens is the excretory duct of the testis.
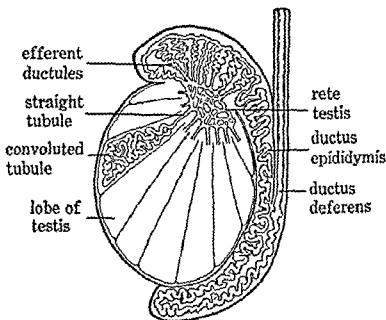
FIGURE 252. Diagram of the relation between the testis, epididymis, and ductus deferens. Modified from Morris' Human Anatomy, J. P. Schaeffer, editor, Blakiston, 1947.

Prepubertal seminiferous tubules. The appearance of the seminiferous tubules is different before and after sexual maturity. At birth and until puberty, they appear as solid epithelial cords. They contain only two types of cells: **indifferent cells** and **spermatogonia.** The spermatogonia are the primary sex cells. The cords develop lumens during puberty, and this converts them into tubules, lined with stratified epithelium of a sort. The subjacent stroma provides a basement membrane for the tubule. Interstitial cells are present in the stroma but do not begin to form their secretion until stimulated by the anterior lobe of the hypophysis. The sex cells increase in number during the years of puberty, and the adult condition of the tubule epithelium is eventually reached. Figures 253 and 254 show the prepubertal condition in the monkey.

Adult seminiferous tubules: The structure of the adult seminiferous tubule is complex because its cells are constantly changing. Like the

bone marrow, the seminiferous epithelium is engaged in mass production of free cells. Its products are the sperm. The process by which they are made is called **spermatogenesis.**

FIGURE 253. Testis of an immature monkey. The outer wall of the tunica vaginalis (tv) is above the cleft at the upper edge of the figure; below the cleft is the heavy tunica albuginea (ta) with an artery (a) in the lower part of it. Seminiferous tubules, with lumens forming, are seen at the lower part of the figure. Photomicrograph, 150 ×

Not all cells of the tubular epithelium form sperm. Some are **supportive cells** (Sertoli) which have irregular shape. As they tower above the basement membrane, they are recognizable in sections by a large vesicular nucleus which stands in contrast with the dark nuclei of developing

sex cells. Supportive cells are indented from the side by the pressure of adjoining spermatogenic cells.

The appearance of seminiferous tubules is shown in Figs. 255 and

FIGURE 254 Prepubertal testis of a monkey The larger, more peripheral nuclei (*spg*) belong to spermatogonia, others are nuclei of indifferent cells Photomicrograph, 600 ×

256. A variable number of layers of cells is concerned with sperm formation. Nearest the basement membrane are the **spermatogonia.** From their mitotic division arise other spermatogonia. No other divisions take place in the prepubertal testis. Several irregular rows are distinguishable in the adult. After many divisions of this type, **primary spermatocytes**

are formed. They are larger cells and lie about midway between the base-
ment membrane and the lumen. By their divisions, **secondary sperma-**

FIGURE 255. Two portions of a seminiferous tubule of a 65-year-old man
Abbreviations are c, connective tissue, s, supportive cells, sp, spermatocytes,
spg, spermatogonia, spt, spermatids, spz, sperm Photomicrograph, 600 ×.

tocytes arise; few are seen in most tubules because they quickly divide
into **spermatids**. These small cells are found in several layers near the
lumen. They have dark nuclei.

Various stages in the transformation of spermatids into **sperm** will be

sex cells. Supportive cells are indented from the side by the pressure of adjoining spermatogenic cells.

The appearance of seminiferous tubules is shown in Figs. 255 and

FIGURE 254 Prepubertal testis of a monkey. The larger, more periph-
eral nuclei (*spg*) belong to spermatogonia, others are nuclei of indiffer-
ent cells Photomicrograph, 600 ×

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in the adult. After many divisions of this type, **primary spermatocytes**

How they get out of the seminiferous tubules and through the rete testis is unknown. Possibly they are flushed along by a fluid transudate from the tubule walls.[1]

Spermatogenesis: The final mitotic division of spermatogonia produces cells that grow into primary spermatocytes during their intermitotic interval. Each has the full number of chromosomes. The number characterizes all body cells of the species. It is 48 in man. The chromosomes are present in pairs. The individuals of 23 pairs are alike, but the pairs vary in shape and size. The twenty-fourth pair consists of two odd chromosomes, called X and Y.

The intermitotic period, between last spermatogonial and first spermatocytic divisions, is one of growth and preparation for an event that occurs nowhere else in the body. The pairs of chromosomes are pulled apart in a special meiotic division of the large primary spermatocytes. One member of each pair goes to each of the secondary spermatocytes. This applies also to X and Y. Thus, there are two kinds of spermatocytes: those with an X plus 23 ordinary chromosomes and those with a Y plus 23 ordinary chromosomes.

The secondary spermatocytes undergo another meiotic division in which each of the 24 chromosomes splits lengthwise in the manner of body-cell chromosomes during mitosis. Thus, four spermatids are formed: two from each of the secondary spermatocytes with reduced number of chromosomes.

No further meiotic divisions take place. The spermatids become transformed into mature sperm during a remarkable metamorphosis which involves loss of cytoplasm, attenuation of nucleus, and development of a long flagellum, or tail. Consult books on embryology or cytology for details of this process.

There are two kinds of sperm in man, but you cannot tell them apart by inspection. The chromatin of one bears the genes of the X chromosome; that of the other, the Y. All ova are endowed with X chromosomes. Fertilization of an ovum by an X-bearing sperm gives rise to a female offspring; fertilization by a Y-bearing sperm, to a male.

There is never, under normal conditions, a time during which spermatogenesis ceases in man, once it has been started at puberty. However, the process of spermatogenesis requires special conditions and cannot be carried out within the abdominal cavity. Body temperature is too high there. During development, the testes with their ducts and blood vessels

[1] See Visual Aids, 43.

seen in different tubules. Groups of immature sperm may be found with
their heads attached to the cytoplasm of supportive cells as though being
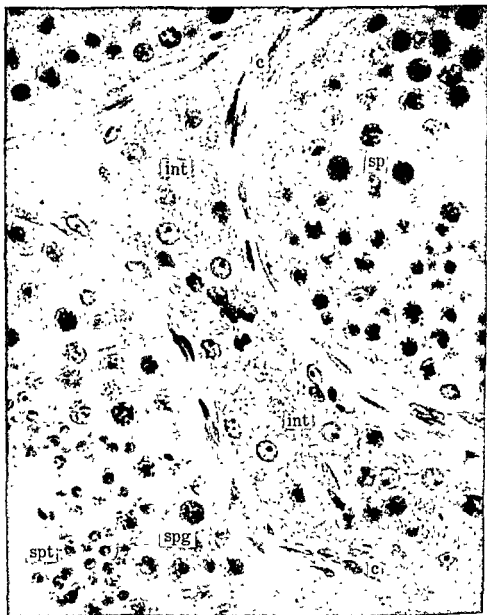
FIGURE 256. Interstitial cells, *int*, wedged between portions of a seminifer-
ous tubule of a 65-year-old man Abbreviations are as in Fig 255 Compare
the several portions of seminiferous tubules in Figs. 255 and 256 for various
stages in spermatogenesis. Photomicrograph, 600 ×.

nursed by them. Not every section through a tubule will have such
groups of nearly ready sperm, because spermatogenesis occurs in waves,
and when one batch has been completed, the sperm quickly leave the
testis to be stored in the epididymis. Sperm are nonmotile at this time.

Interstitial cells: Endocrine function of the testis appears to be vested in the **interstitial cells** (Leydig). These are irregularly polyhedral cells occurring individually or in clumps in the stroma between seminiferous tubules. They are easily identified by their size, for they are about 15 to 20 μ in diameter, which is greater than most other connective-tissue elements. Fat is lacking. Lipoid droplets, granules, and certain crystalloid bodies are sometimes seen in the fresh state, although you may not observe them. Interstitial cells are shown in Fig. 256.

Hormones produced are androgens, **testosterone** being the specific name given to the male sex hormone. The endocrine secretion of the testis greatly influences not only the genital organs but many other organs and tissues of the body. It is specifically concerned with development and maintenance of secondary sexual characteristics and the sex organs. It is the masculinizing hormone. Endocrine secretion of the testis is controlled by the anterior lobe of the hypophysis.

Straight tubules and rete testis: The seminiferous tubules end abruptly at the mediastinum by joining short **straight tubules**, lined with simple columnar epithelium. The basement membrane disappears. There is no smooth muscle but only dense connective tissue around them.

The straight tubules enter anastomosing channels of similar structure. The lining of some of them is low columnar epithelium. An occasional cell may show a single flagellum extending from its surface. These channels form the **rete testis**, shown in Fig. 257.

EPIDIDYMIS

The **efferent ductules**, a dozen or more in number, enter the head of the epididymis. They join it with the rete testis and carry the sperm into their storage depot. Some storage may take place in the efferent ductules themselves. They are the first tubules to exhibit secretory characteristics. Efferent ductules *are convoluted and may be 6 cm. in length.* They are shown in Fig. 258.

A basement membrane reappears, and the epithelium is very characteristic. It is composed of alternating longitudinal strips of low and high columnar cells, with some pseudostratified regions in which a few basal cells occur. Low cells may display a flagellum. High cells tend to be ciliated. The cilia are active and beat toward the epididymis. Cells display secretory activity. Sperm acquire the capacity for motility in the efferent ductules and epididymis. Beneath the basement membrane of

descend into the scrotum, where the temperature is 1.5 to 3 deg.
lower.

The **scrotum** is simply a sac of thin skin with extra pigment in the

FIGURE 257. Human rete testis (65-year-old). Photomicrograph, 150 ×.

epidermis and bundles of smooth muscle replacing fat in the corium.
Cold contracts the muscles and wrinkles the skin. Heat has the opposite
effect. Thus, there is provided a temperature-regulating mechanism
which is important for spermatogenesis.

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stored. It is a long (4 to 6 meters), narrow (0.4 mm.), convoluted tube, receiving the efferent ductules at the upper pole and joining the ductus
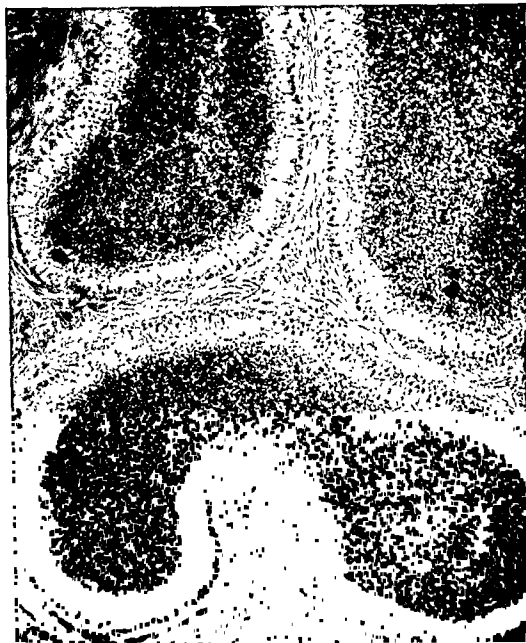
FIGURE 259. Epididymis of a young man. The tubules are full of sperm which stain darkly. The epithelium, of secretory columnar cells, stains lightly with a connective-tissue stain. Photomicrograph, 150 ×.

deferens at the lower pole of the testis. It is lined by tall pseudostratified epithelium displaying two rows of nuclei. On the surface are extensions of the intercellular cement substance which have been described and

the efferent ductules are a few smooth-muscle cells forming a thin circular layer in the lamina propria, which is more prominent toward the epididymis.
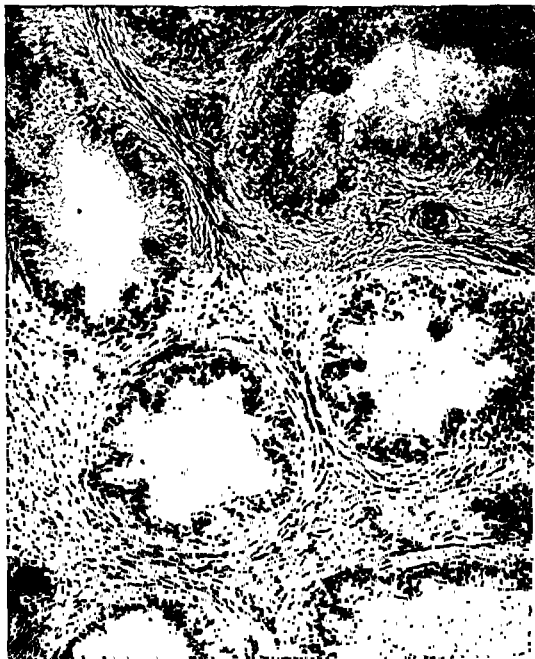
FIGURE 258. Efferent ductules of a young man. Photomicrograph, 150 ×.

The **epididymis** proper is the main sperm storage depot. It is shown, full of sperm, in Fig. 259 The epididymis also adds its very essential secretion to the fluid medium in which the sperm are activated and

normally proceed through the excretory ducts. Between emissions, sperm that find their way much beyond the epididymis die in the ductus deferens.

SEMINAL DUCTS

The sperm-transporting ducts are the ductus deferens, ejaculatory ducts, and urethra. They are not primarily concerned with secretion, although that function is not excluded.
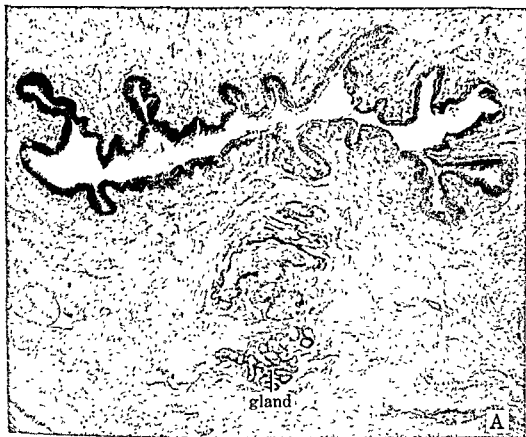
gland

FIGURE 261A Cavernous urethra; the lumen with branching lacunae is surrounded by erectile tissue in which is embedded a urethral gland. Photomicrograph, 40 ×.

Ductus deferens: The epididymis gradually changes in structure at the lower pole of the testis where it turns upward to become the **ductus deferens.** Convolutions diminish and muscle increases. Its epithelium changes from pseudostratified to tall simple columnar. Toward the ejaculatory duct, it may become stratified. The lumen is wider than that of the epididymis and widens even more at the lower end to form the **ampulla.** The epithelium is thrown into longitudinal folds and has a little connective tissue beneath it, forming a lamina propria and basement

pictured by histologists as nonmotile cilia (Fig. 25). Beneath the epithelium are a basement membrane and a lamina propria containing a very

FIGURE 260. Human ductus deferens. Note the stereocilia on the surface of the epithelium; also note 1, inner longitudinal muscle bundles, 2, thick circular muscle layer, and 3, outer longitudinal muscle. Photomicrograph, 150 ×.

thin layer of circular smooth muscle. During ejaculation, 200 million or more of the stored sperm are forced out of the epididymis into the ductus deferens by action of this smooth muscle. Only at this time do sperm

cessed, and it is lined with simple columnar or pseudostratified epithelium, becoming transitional at the urethral end. Muscular layers are absent, and the wall is made up of dense fibrous connective tissue in the stroma of the prostate gland. The two ejaculatory ducts run for about 1.5 or 2 cm., converging toward the urethra where they open by extraordinarily minute pores (Fig. 262).

FIGURE 262. Colliculus seminalis in the human prostatic urethra. The crescentic cleft is the lumen of the urethra; the two fenestrated areas in the colliculus are the ejaculatory ducts, one of which is seen opening into the urethra on the right. The blind end of the utriculus prostaticus may be seen at *u*. Photomicrograph, 35 ×.

Urethra· The only part of the male **urethra** corresponding to that of the female (page 372) lies between the bladder and the openings of the ejaculatory ducts. The structure of this part is the same in both sexes. The rest of the male urethra is a duct for transporting semen as well as urine.

There are three parts of the male urethra: **prostatic, membranous,** and

membrane. The rest of the wall is principally smooth muscle arranged in inner and outer longitudinal layers with a circular layer in between. The ductus deferens is illustrated in Fig. 260.

Surrounding the ductus deferens is a great deal of areolar connective tissue containing lymphatics, an extensive venous plexus, the spermatic

FIGURE 261B. *Cavernous urethra: a detail from the left end of 261A. Photomicrograph, 150 ×.*

artery, nerves, and bundles of skeletal muscle (cremaster). The pampiniform veins have unusually thick walls with longitudinal and circular smooth muscle. All these structures comprise the **spermatic cord**, which traverses the abdominal wall via the inguinal canal.

The **ampulla** of the ductus deferens is a dilation, in which the longitudinal folds of mucosa are exaggerated and intervening depressions form deep valleys as well as diverticula. Some of the lining epithelium appears to be secretory. The muscular layers are irregularly arranged.

Ejaculatory ducts: The ampulla of the ductus deferens and the short duct of the seminal vesicle unite to form the **ejaculatory duct**. The mucous membrane resembles that of the ampulla. It is thin, folded, and re-

the **prostate gland** (Fig. 262). The ejaculatory ducts likewise traverse it. The prostate is really a mass of fibrous and muscular tissue in which

FIGURE 263. Human seminal vesicle. Photomicrograph, 150 ×

30 to 50 small compound tubulo-acinous serous glands are embedded (Fig. 264). These glands vary greatly in form and size. Lumens are large and irregular in the acini—which are so dilated as more properly

cavernous. Near the bladder the epithelium is transitional. Near the external orifice, where there is a dilation called the **fossa navicularis**, it is stratified squamous. Elsewhere, throughout most of the length of the urethra, the mucous membrane has pseudostratified epithelium. Patches of stratified squamous epithelium are commonly present. Mucous cells, found in this epithelium, form small glandular pouches or **lacunae** in some places. Into these lacunae open the mucous **urethral glands** (Littré).

Muscle is present in the prostatic and membranous parts of the urethra as inner longitudinal and outer circular layers. Longitudinal fibers continue into the proximal part of the cavernous urethra. Fibrous connective tissue forms a lamina propria containing capillaries and venules. It is rich in elastic fibers.

A prominent dorsal longitudinal fold of mucosa in the prostatic urethra mounts an elevation known as the **colliculus seminalis**, on which the pore-like openings of the ejaculatory ducts appear. At the middle of the colliculus there is a little blind pocket, the **utriculus prostaticus**, which is homologous with the vagina in the female (Fig. 262).

SEMINAL GLANDS

Three groups of glands which contribute ingredients of the semen are seminal vesicles, prostate gland, and bulbourethral glands. The first two are of greatest importance in providing an alkaline buffer solution to neutralize acid vaginal secretions and enhance sperm activity.

Seminal vesicles. The structure of the **seminal vesicle** is similar to that of the ampulla of the ductus deferens (Fig. 263). It is an irregularly coiled saccular appendage of the ductus deferens. The epithelium is extensively folded, and numerous crypts are formed. Cells of the epithelium are columnar and mainly pseudostratified, containing yellowish lipochrome pigment after puberty. They secrete a yellow viscous fluid.

In and beneath the folds of epithelium is loose fibrous connective tissue forming a lamina propria. Muscular coats are very thin, mainly circular. An outer layer of connective tissue, blending with that of the bladder, may contain small autonomic ganglia.

The presence of sperm in the lumen of the seminal vesicles is no proof that they are stored in this gland. It is probable that their appearance there after death is artifactual.

Prostate gland: Surrounding the urethra at the neck of the bladder is

concretions are formed in the prostatic secretion, which is an alkaline fluid of thin consistency imparting the specific odor to the semen.

The **prostatic stroma** contains smooth-muscle fibers throughout the

FIGURE 265. Lamina albuginea (above) and a portion of the adjacent corpus cavernosum penis, adult human. The cavernous vascular channels are partly filled with darkly staining blood. Photomicrograph, 35 ×

gland. These occur in layers or bundles, but also singly. Nerve fibers, blood vessels, and lymphatics traverse the stroma. Small ganglia of autonomic nerve cells may be found. The whole organ is encapsulated by fibrous connective tissue containing smooth muscle.

Bulbourethral glands: Two small compound tubulo-acinous, mucous, **bulbourethral glands** (Cowper) pour their secretion into the beginning

to be called alveoli—and small in the tubular portions. Numerous ducts open into the urethra. The epithelium is simple columnar, varying in height.

FIGURE 264. Lobule of the prostate gland of a young man. Photomicrograph, 150 ×.

Within the alveoli may be found some eosinophilic **prostatic concretions**, sometimes lamellated in old age. These may begin to appear in middle age but are rarely found in the early postpubertal period. The

concretions are formed in the prostatic secretion, which is an alkaline fluid of thin consistency imparting the specific odor to the semen.

The **prostatic stroma** contains smooth-muscle fibers throughout the

FIGURE 265 Lamina albuginea (above) and a portion of the adjacent corpus cavernosum penis, adult human The cavernous vascular channels are partly filled with darkly staining blood Photomicrograph, 35 ×.

gland. These occur in layers or bundles, but also singly. Nerve fibers, blood vessels, and lymphatics traverse the stroma. Small ganglia of autonomic nerve cells may be found. The whole organ is encapsulated by fibrous connective tissue containing smooth muscle.

Bulbourethral glands: Two small compound tubulo-acinous, mucous, **bulbourethral glands** (Cowper) pour their secretion into the beginning

of the cavernous urethra by short ducts. They lie on either side of the membranous urethra.

FIGURE 266 Arteries of the adult penis surrounded by cavernous spaces containing darkly stained blood Note the heavy intima with the lumen almost occluded Photomicrograph, 150 ×.

PENIS

The essential parts of the copulatory organ are three cavernous bodies and the urethra. The rest of the penis is composed of fibrous connective tissue and skin. A bone is present in some animals to supplement an in-

adequate vascular erectile mechanism. The penis lacks fat cells and is well supplied with afferent nerve endings.

The **corpora cavernosa penis** are the two principal erectile bodies. Surrounded by a double layer of dense fibrous connective tissue, the **lamina albuginea**, they are incompletely separated from each other by a septum of this same connective tissue. Figure 265 illustrates the lamina and adjacent erectile tissue.

The **corpus cavernosum urethrae** is a similar erectile mass surrounding the urethra (Fig. 261). It begins as a bulbous enlargement at the membranous urethra, has a narrow shaft, and spreads out at the end of the penis to form a cap, the **glans**, which is covered with a thin skin.

The corpora cavernosa are supplied by very peculiar **tortuous arteries** which have bands of longitudinal smooth muscle bulging into the lumen (Fig. 266). Most of the time, the circular smooth muscle is contracted, and the pads formed by the longitudinal muscle block the arterial lumen. Vasodilation of the coiled arteries, initiated by the nervous system, brings about erection. The veins draining the cavernous bodies have valves that tend to retard blood flow. The intervening channels are mere endothelium-lined clefts in the flaccid penis (Fig. 265). However, during erection, these fill with blood under arterial pressure and stiffen the cavernous bodies against the surrounding lamina albuginea. After ejaculation, vasodilation is inhibited, the arterial muscle resumes its tonus, blood no longer engorges the cavernous spaces, and flaccidity is resumed.

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   Changes in the prostate with aging are especially important.

Female Reproductory Organs

The female reproductory organs are the ovaries, in which egg cells and sex hormones are formed; and the uterine tubes, uterus, and vagina, which are for the reception and transportation of ovum and sperm. The uterus displays cyclical changes correlated with endocrine activity of the ovary. Each month, during the childbearing period, it prepares itself for implantation of the fertilized ovum. It exhibits remarkable adaptability in accommodating the growing fetus during pregnancy.

Female external genital organs are homologous with those of the male and exhibit no new structural feature of consequence. The mammary gland is an important accessory organ of reproduction. It will be considered in Chap. 25.

OVARY

The ovary is a little smaller and flatter than the male gonad. It lies within the peritoneal cavity, attached by a fold of peritoneum, the mesovarium, to the broad ligament of the uterus. It has no intrinsic duct nor tubules like the testis and consequently lacks a glandular appearance, even though it has endocrine functions. Figure 267 illustrates the appearance of the ovary in cross section.

Ovarian epithelium: The epithelium on the surface of the ovary is continuous with the mesothelium of the peritoneal cavity, but it is low columnar instead of squamous It is the **germinal epithelium** from which arise all the ova.

Ovarian stroma: A layer of dense fibrous connective tissue forms a collagenous capsule, the **tunica albuginea**, just beneath the germinal epithelium. The **mesovarium**, or mesentery of the ovary, attaches to the hilus, and its looser connective tissue carries blood vessels, lymphatics,
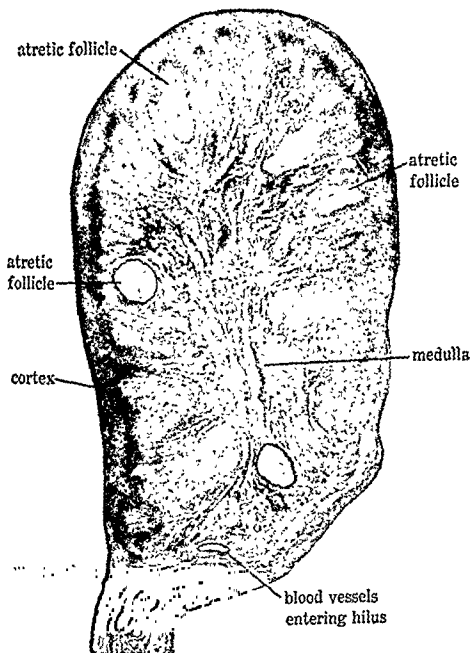
FIGURE 267. Human ovary during puberty. The cortex is full of primary
follicles which are invisible at this low magnification. Several stages in
atresia of prematurely developed follicles can be seen. Specimen in the
Piersol collection, carmine stain. See *Piersol's Normal Histology*, 14th ed.,
Fig 303, Lippincott, 1929. Photomicrograph, 5 ×.

and nerves into the hilus to form a central portion, the **medulla** of the
ovary. Some smooth-muscle fibers are present in the medulla.

Peripherally, the stroma of the ovarian **cortex** exhibits an unusually

FIGURE 268. Cortex of the ovary of a ⸺ ⸺ ⸺ ⸺ ⸺ al epi-
thelium on the surface and many primary follicles embedd⸺ ⸺ ⸺ cellular
stroma. Photomicrograph, 150 ×.

cellular appearance. In fact, it has an appearance that is characteristic
even when oöcytes and follicles are not seen, because it is filled with
spindle-shaped connective-tissue cells. Although there are collagenous
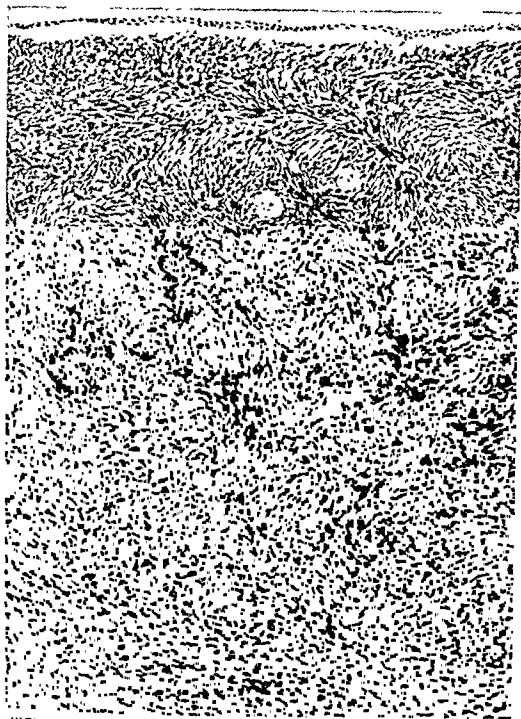
FIGURE 269 Cortex of the ovary after puberty (14-year-old girl). The epithelium has become artificially separated from the subjacent tunica albuginea. Two primary follicles are visible. Photomicrograph, 150 ×.

and reticular fibers in the cortical stroma, elastic fibers are scarce. The spindle-shaped cells resemble smooth-muscle fibers, but they lack fibrils in their cytoplasm and are not contractile. They are special connective-

tissue elements, and some of them become the thecal cells around the ovarian follicles as the latter enlarge. Their appearance is illustrated in Figs. 268 and 269.
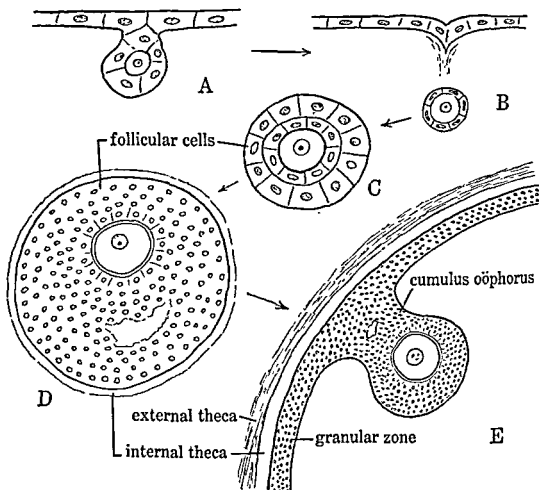
FIGURE 270. Diagram of the formation and maturation of a Graafian follicle: budding cell group from germinal epithelium of embryonic ovary, A, primary follicle, B, growing follicle, C; early stage in formation of a vesicular follicle, D; maturing follicle, E.

Prepubertal ovary: The size and appearance of the ovary varies with age. At birth, it is small and contains only oöcytes derived from the germinal epithelium during prenatal life. You should consult an embryology textbook for a description of this process. In the embryo, clusters of cells bud off from the epithelium and become buried in the stroma. These are primordia of **oögonia** and **follicular cells.** After further mitotic division, one cell in each cluster enlarges and becomes an **oöcyte.** The rest form small flat follicular cells around it. The cortex of an infant's ovary is shown in Fig. 268.

At birth, there may be as many as a half million of these **primary folli-**

cles in the two ovaries. Only about 400 will reach maturity and ovulate. The rest of the oöcytes degenerate, the follicles undergoing **atresia**[1] at various stages in their development. Atresia takes place before as well as after puberty. Compare the cortex of the infant's ovary with that of a 14-year-old girl (Fig. 269). Since the ovary grows in size as the number of follicles declines, sections through it will display fewer follicles at the time of puberty than at an earlier time.

The prepubertal ovary has the characteristic cellular stroma. Its cortex contains primary follicles, all measuring about 40 μ in diameter; the oöcyte in each is about 20 μ in diameter. Rarely does any one of the primary follicles of the prepubertal ovary undergo significant growth in size. The prepubertal ovary has no endocrine function.

Prime postpubertal ovary: During the years after puberty, throughout the childbearing period and until the menopause is reached, the ovary undergoes cyclical changes that alter its structure markedly. The changes to be considered are follicular growth, follicular atresia, ovulation, formation of corpora lutea, regression of corpora lutea, and the scar formation that follows. The ovary changes from a smooth pink body to a wrinkled grayish mass during the childbearing period.

Follicular growth begins with puberty, and both are initiated by the anterior lobe of the hypophysis which starts to secrete gonadotropic hormones. After ten to fourteen years of intermitotic rest, some of the oöcytes of the primary follicles enlarge, and their peripheral follicular cells proliferate to form a stratified layer (Fig. 270). The surrounding connective-tissue cells form a cellular capsule, the **theca**. As the follicular cells build up a thick layer, follicular fluid begins to accumulate in a small cavity among them. This cavity is destined to enlarge, as the whole follicle grows, and the follicular fluid increases in amount.

A primary follicle thus becomes a **vesicular follicle** (Graaf). The oöcyte is then seen in a clump of follicular cells, the **cumulus oöphorus,** on one side of the relatively huge cavity lined with stratified follicular epithelium. The lining is called the **membrana granulosa.** A thick basement membrane separates this epithelium from the theca, formed by encapsulating connective-tissue cells. The theca of a mature follicle has two layers: the internal theca is vascular; the external theca, fibrous. The maturing vesicular follicle, commonly called Graafian follicle, is illustrated in Fig. 271.

The oöcyte has a diameter of 0 1 to 0 15 mm just before ovulation.

[1] Here the term atresia signifies an abortive phenomenon in which the follicle dies and degenerates.
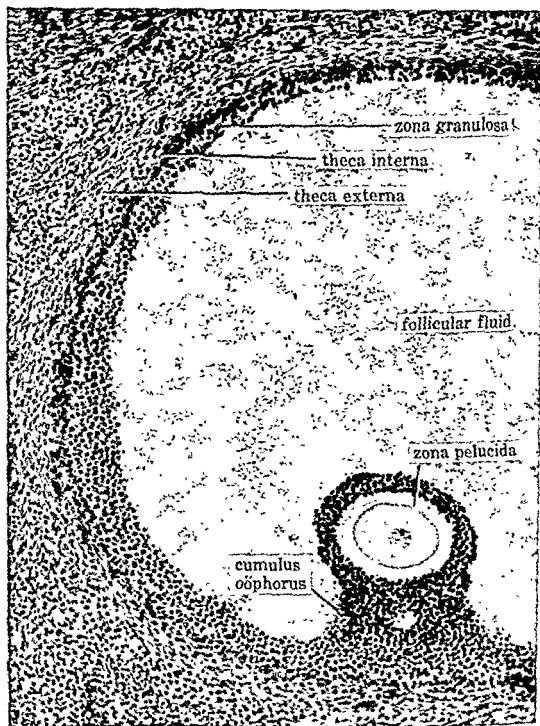
FIGURE 271. Graafian follicle in a cat's ovary. Photomicrograph, 150 ×.

Yolk granules are found in its cytoplasm. The follicle *cells* are separated from the oöcyte by a thick homogeneous membrane called the **zona pellucida.**

Many stages in the development of *follicles* can be found in serial

sections of the ovary of a young woman. However, toward the end of the childbearing period, sections of the ovary will display few, indeed. If you confine your study to ovaries of laboratory animals, such as the cat, you are apt to form a misconception of the number of follicles present in the human, because their ovaries are filled with oöcytes, whereas these cells are scattered in the adult human ovary.

When the vesicular follicle reaches its greatest magnitude, it measures 10 to 12 mm. in diameter. No longer is it buried deeply in the ovarian stroma; it now encroaches upon the surface epithelium. The tunica albuginea becomes thin and avascular at one point, which is called the **stigma.** There, rupture of the follicle will take place. Additional spaces form among the follicular cells of the cumulus oophorus, and the oocyte with an encapsulating layer of follicular cells is loosened from the membrana granulosa. The surrounding follicular cells look like a radiating crown, when viewed through a microscope, and are called the **corona radiata.**

Ovulation takes place when pressure of follicular fluid has built up and the stigma become thin enough for the rupture point to be reached. This occurs at about the middle of the menstrual cycle; the time is variable by several days each way. The follicular fluid oozes from the opening. This causes the dislodged **ovum,** surrounded by corona radiata, to be washed out into the abdominal cavity.[2]

Ovulation releases one ovum, as a rule, although two follicles may ovulate on occasion. The two ovaries usually alternate at intervals of approximately twenty-eight days. The liberated ovum finds itself in close proximity to fimbria of one uterine tube and immediately enters the tube. There, fertilization can take place.

A **mature ovum,** like a sperm, has half the somatic number of chromosomes. The **oögenia** are formed in the fetus by repeated divisions of primordial germinal cells. At the time of birth, all are undergoing the intermitotic growth that characterizes them as oocytes.[3] After puberty, **primary oöcytes** one by one undergo *a meiotic division* which reduces the number of chromosomes by separating the pairs. Unlike the first meiotic division in the male gonad, two **secondary oöcytes** are not formed. The cytoplasmic division is uneven, resulting in one secondary

[2] See Visual Aids, 44.

[3] It is possible that oogonia are formed from new ingrowths of germinal epithelial cells after birth. Some investigators believe that all the original oogonia of the fetus are doomed to degenerate and that all ova that are formed in the adult arise from this new development from the germinal epithelium.

FIGURE 272. *A*, human ovary showing vesicular follicles undergoing atresia; *B*, corpus luteum of menstruation in a human ovary. Photomicrographs, 6 ✕.

oöcyte and one diminutive cell called a **polar body.** Similarly, the meiotic division of the secondary oocyte leads to formation of one **ovum** and a second polar body. The first polar body does not bother to divide

FIGURE 273. Adult human ovary showing degeneration of a corpus luteum of menstruation with many darkly stained blood vessels around it, a large corpus albicans and several older smaller ones are shown. Compare with Figs. 267 and 272. Photomicrograph, 6 ×

in most species of animals. Polar bodies degenerate. Exact times of polar body formation are unknown in man. Probably the first division occurs in the ovary and the second division after ovulation, as it does in some other species of animals.

FIGURE 272. *A*, human ovary showing vesicular follicles undergoing atresia; *B*, corpus luteum of menstruation in a human ovary. Photomicrographs, 6 ×.

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FIGURE 273. Adult human ovary showing degeneration of a corpus luteum of menstruation with many darkly stained blood vessels around it, a large corpus albicans and several older smaller ones are shown. Compare with Figs 267 and 272 Photomicrograph, 6 ×.

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Atresia is the fate of most oöcytes. Primary follicles degenerate and disappear completely. After a follicle has begun to grow, atresia is followed by the formation of a scar in the ovarian stroma. The more advanced in development, the greater the size of the scar. Oöcyte and follicular cells undergo physiological degeneration. The zona pellucida becomes folded and may remain visible for some time.

Nearly matured follicles undergoing atresia display other changes. The degenerating membrana granulosa is replaced by loose fibrous connective tissue, even before the zona pellucida has disappeared. The cells of the internal theca at first become swollen, are filled with lipoid droplets, and are arranged in cords or radial strands, resembling the theca lutein cells of the corpus luteum. The thick basement membrane of the membrana granulosa persists. **Corpora atretica** in various stages of development and decline may be found in most sections of the ovary.

A **corpus luteum** results from transformation of the ruptured mature follicle (Fig. 272). A potent hormone from the anterior lobe of the hypophysis is responsible for this. The wall of the follicle collapses and becomes folded after ovulation. The follicular cells change their appearance by enlarging greatly and arranging themselves in cords. The cells stain more lightly, and their cytoplasm gradually develops lipochrome granules that impart a pale-yellowish color to the fresh corpus luteum.

Vascularity of the corpus luteum is provided by the internal theca. Cells of this layer likewise enlarge and form masses in the recesses between the folds of the transformed follicular cells. Two types of lutein cells are present: the **granulosa lutein cells** and the **theca lutein cells**.

The **corpus luteum of menstruation** is a transient structure which begins involution two weeks after ovulation has occurred. Its lutein cells undergo fatty degeneration and are replaced by connective tissue of the loose variety. Several weeks later the site is marked by a small scar called a **corpus albicans** (Fig. 273).

The **corpus luteum of pregnancy** differs from that of menstruation in size and duration. It may be 2 to 3 cm. in diameter and produces a marked bulging on the surface of the ovary. Indeed, it is an endocrine gland of considerable magnitude. It does not begin involution until about the fifth or sixth month of gestation.

The **endocrine function** of the ovary is served by the follicular cells as well as the corpus luteum. The secretion of the follicular cells stimulates development of the genital organs and secondary sexual characteristics when it is first formed at the time of puberty. The follicular hormone,

FIGURE 274. Corpus luteum; a detail from the specimen shown in Fig 272B. Abbreviations are *st*, stroma, *th*, theca lutein cells; *gr*, granulosa lutein cells. Photomicrograph, 150 ×.

estrone, is produced under influence of the hypophysis. It is produced in quantity and excreted in the urine. As estrone increases with the growth of the follicle, it causes the hypophysis to reduce production of its **follicu-**

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lar stimulating substance. A **luteinizing** fraction from the hypophysis then dominates. This brings about transformation of the granulosa cells to lutein cells after ovulation.

The hormone produced by the corpus luteum is **progesterone**. Its secretion overlaps that of estrone. Progesterone prepares the uterine mucosa for implantation of a fertilized egg. Its production is brief unless fertilization takes place. The suprarenal cortex and the placenta are other sources of progesterone.

FIGURE 275. Human uterine tube; ampulla. Photomicrograph, 35 ×.

Postmenopausal ovary: Cyclical production of ova continues for thirty or forty years before it gradually subsides and is followed by the **menopause**. Ovarian hormones are no longer formed when this occurs, but the hypophysis goes on producing its follicular stimulating hormone in increased amounts. The ovary at this time has become a wrinkled fibrous body containing scars but no follicles. The typical ovarian stroma is abundant.

UTERINE TUBE

Each **uterine tube** (Fallopius) is about 15 cm. long and 10 mm. in diameter, has a free end near the ovary, and buries itself in the upper end

of the uterus. Structural appearance varies according to distance away from the uterus. Three general regions are recognized in the uterine tube. A narrow **isthmus** forms the medial one-third, a widening makes up the outer two-thirds, and a dilated funnel opening surrounded by finger-like projections imparts the name **infundibulum to the fimbriated end.** Like most tubular organs, the uterine tube has tunica mucosae, tunica muscularis, and tunica serosa, but it lacks a true submucosa and there is no muscularis mucosae.
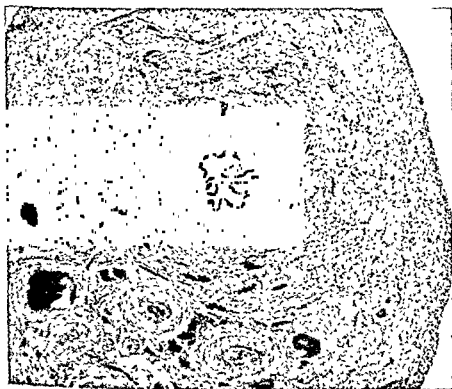
FIGURE 276. Human uterine tube; isthmus. Photomicrograph, 35 ×.

The mucous membrane of the uterine tube has a lamina propria composed of rather cellular and vascular fibrous connective tissue upon which a simple columnar epithelial lining is placed. It is highly and irregularly folded. In the ampulla, the folding is much exaggerated and becomes complex (Fig. 275). In the isthmus, the folding is less marked (Fig. 276).

Cells of the epithelium are of two types. Some of them are ciliated (Fig. 23). The nonciliated cells are secretory and may provide the ovum with a fluid vehicle for its passage down the tube. The cilia beat toward the uterus and supplement muscular contraction of the uterine tube as a means of transporting the fertilized ovum. Sperm ascend the uterine tube against this ciliary stream. The height of the epithelium of the tubu-

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FIGURE   ., longitudinal section from a 38-year-old woman, showing heavy myometrium, *myo*, and thin endometrium, *end*, in proliferative phase of cycle, *B*, longitudinal section, 12-year-old girl, showing thinner myometrium; *C*, transverse section through body of a human uterus early in pregnancy Photomicrographs, 4 ×.

lar mucosa changes cyclically in response to the ovarian hormones, along with that of the uterus. Although the complicated mucosal foldings suggest a glandular structure, no glands are present in the uterine tube.

The **tunica muscularis** consists of two layers: a thin outer longitudinal and a thicker inner circular or spiral layer. They are not sharply delimited from each other. The muscular layers are thickest at the uterine end of the isthmus.

UTERUS

The uterus is a thick tubular organ representing the fused lower part of two embryonal ducts from which the uterine tubes arise. Its basic structure—mucosa, muscularis, and serosa—resembles that of the uterine tubes. The epithelium of the uterus is similar. Otherwise, the uterus is quite unlike other tubular organs, and especially so during the postpubertal years of active ovarian function, when profound cyclical variations in uterine structure are the rule.

Two portions of the uterus differ markedly. The **cervix** or lower end, including the part projecting into the vagina, maintains a fairly constant structure. The rest of the organ, made up of **isthmus** and **body** (including **fundus**), exhibits maximal variations during menstrual as well as pregnancy cycles.

Prepubertal uterus: At birth, the uterus is larger in relation to the entire body than it is in the adult. It immediately undergoes a size reduction correlated with withdrawal of the influence of the mother's estrogenic hormones. Thenceforth until puberty, the uterus remains unchanged. Cervix and body are approximately of equal length.

The prepubertal uterus has a thick muscular coat covered with peritoneum where it lies in the pelvic cavity. It is lined with a rather highly cellular lamina propria and a simple columnar surface epithelium. Simple tubular glands project from it down into the connective tissue of the lamina propria. The uterine lumen is small. Figure 277B illustrates the structure of the uterus in childhood.

Postpubertal uterus: With the onset of estrone and progesterone secretion at puberty, the uterus as well as other reproductive organs undergo hypertrophy. The uterus begins to display its characteristic structural changes at irregular intervals of approximately twenty-eight days.[4] These cyclical changes continue until the menopause.

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[4] The length of the menstrual cycle may vary widely from the traditional period of twenty-eight days under normal conditions. This is especially true during the early years after puberty.

endometrial stroma. The ends of these glands lie in the basal portion of the endometrium and are forked and slightly convoluted. Secretion of a thin fluid substance is sparse. The endometrial stroma contains no coiled arteries in its outer portion during this phase. Only capillaries are present there. Figure 278B shows the endometrium in the proliferative phase.

The **progravid phase**, from approximately the fifteenth to the twenty-eighth day, corresponds to the period of corpus luteum development and progesterone secretion in the ovary. The endometrium more than doubles in thickness, reaching 4 or even 5 mm. by the end of this phase Not only is it thickened; it becomes edematous and full of long dilated and tortuous uterine glands. Their abundant secretion contains glycogen. Coiled arteries make their appearance in the outer layer of the endometrium. The stroma between glands in the deep spongy portion is relatively reduced. Near the surface of the endometrium, the stroma is more compact. Figure 279 shows the uterus late in the progravid phase.

The endometrium is ready to receive a fertilized ovum at the end of the progravid phase. Should fertilization and implantation take place, the progravid phase becomes a **gravid phase** and the endometrium continues its development In the absence of an implanting ovum, the corpus luteum begins to undergo involution. This is the signal to break down the receptive endometrium and start all over again.

A significant change in vascularity of the endometrium occurs a day or so before the beginning of the menstrual flow. Intermittently, contraction of muscle in the coiled arteries deprives the outer zone of the endometrium of blood and oxygen This renders the superficial part ischemic for periods of time that gradually lengthen. These ischemic intervals initiate destruction of the outer part of the endometrium. Lymphocytes invade the stroma in numbers

The **menstrual phase** occupies the first three or four days of bleeding. Figure 278A illustrates the second- or third-day endometrium. As the progesterone stimulus declines, with the beginning of corpus luteum involution, walls of capillaries and some of the coiled arteries give way. Bleeding then takes place into the stroma of the superficial layer of the endometrium. Pieces of the superficial layer are split off by lakes of this blood. They tear away and open other vascular channels.

Contraction of the musculature of the coiled arteries, likewise prevents excessive hemorrhage. No more than 35 cc of blood is lost, as a rule. The blood oozes. It does not spurt. It clots, and the clot is liquefied by a proteolytic enzyme. The menstruum

The two main layers of the wall of the uterine body and isthmus are known as endometrium and myometrium. The *endometrium is the mucous membrane*. Its changes are more pronounced than those of the smooth muscle of the myometrium. Compare Figs 277A and C.

The *endometrium* is lined with simple columnar epithelium containing groups of ciliated cells here and there. The cilia beat toward the vagina. Most of the nonciliated cells are secretory. Simple or slightly branched tubular **uterine glands** extend down through the endometrium toward the myometrium. They are embedded in a thick vascular and highly cellular lamina propria, known as the *endometrial stroma.*

The blood vessels in the endometrial stroma are important and have certain features worth noting. Arteries enter the basal portion of the endometrium and spray or fan out into the stroma, giving rise to arterioles and a very rich network of capillaries. The arterioles that pass toward the surface are convoluted and are sometimes spoken of as **coiled arteries.** They have an unusual structure. Bands of longitudinal smooth muscle lie beneath the tunica intima along one side of their lumen. Contraction of this longitudinal muscle bends them and can retard blood flow.

Basally, other tufts of arterioles and networks of capillaries supply that portion of the endometrium which undergoes the least modification during the menstrual cycle.

Changes in the endometrium during the menstrual cycle may be considered in four phases. These phases are purely arbitrary, and some histologists prefer other classifications.

The **proliferative phase** corresponds to the period of follicular growth stimulation in the ovary It is brought about by an increasing ovarian secretion of esterone. The proliferative phase begins at the end of a menstrual flow, which is approximately the fifth day after its onset. It consists of a reconstitution and slow growth in thickness of the outer layer of the endometrium, *i e.,* the portion that had been sloughed at the preceding menstrual phase The proliferative phase continues until approximately a day after ovulation, *i.e*, until about the fifteenth day after the onset of menstruation.[5]

During the proliferative phase, the simple columnar surface epithelium of the uterus contains a few ciliated cells and many nonciliated cells, most of which are secretory. The cilia sweep fluid and cellular detritus toward the vagina. Uterine glands are thin tubes *surrounded by the*

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[5] Bear in mind that times are approximate.
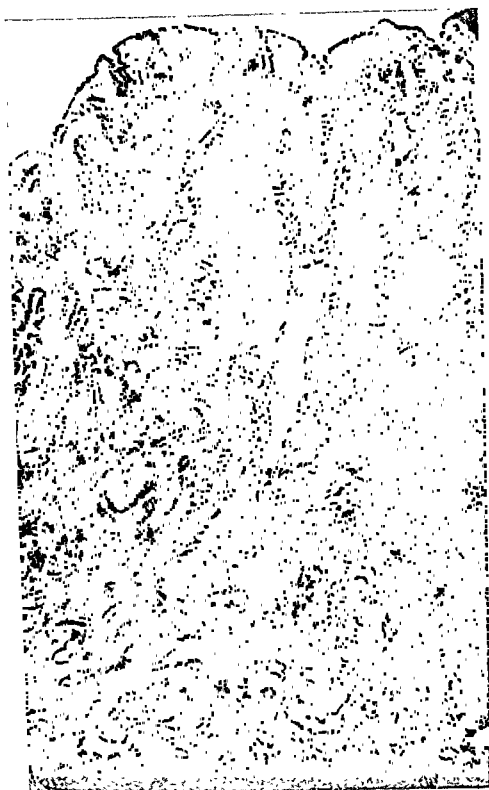
FIGURE 279. Endometrium of human uterus during the progravid phase.
Compare with Fig. 278, A and B Photomicrograph, 40 ×.

FIGURE 278. Endometrium of the human uterus: *A*, second or third day of menstrual cycle (from a specimen loaned by Prof. S. I. Kornhauser); *B*, proliferative phase of the cycle; *C*, postmenopausal endometrium showing cystic glands. Photomicrographs, 40 ×.
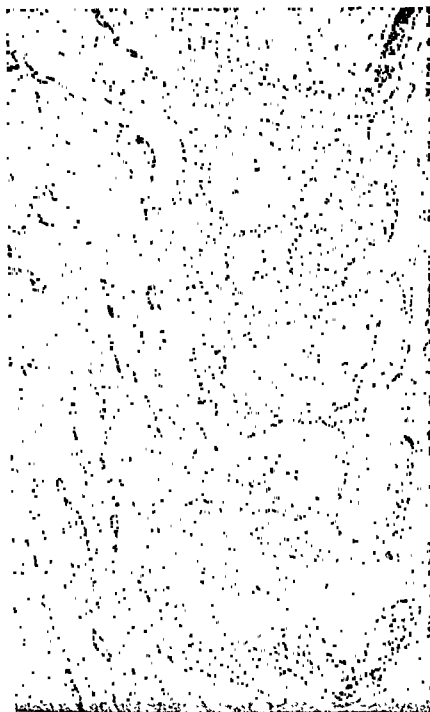
FIGURE 281. Cervix of the human uterus. The section was cut tangentially in respect to the lumen of the cervix. The tall mucous cells of the glands stain lightly. Photomicrograph, 40 ×.
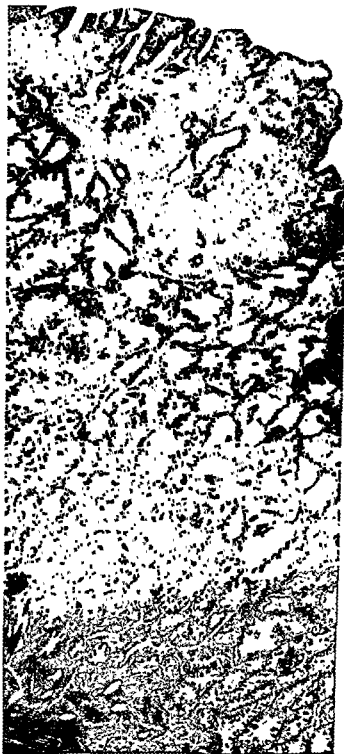
FIGURE 280 Endometrium of the uterus early in pregnancy. This is a detail from Fig 277C Note that the thickness of the endometrium has made it necessary to reduce the size of the photograph by about one-third. Photomicrograph, 25 ×.
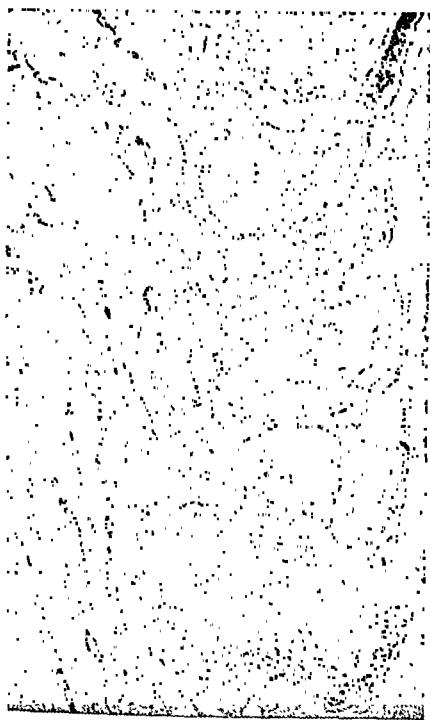
FIGURE 281. Cervix of the human uterus. The section was cut tangentially in respect to the lumen of the cervix. The tall mucous cells of the glands stain lightly. Photomicrograph, 40 ×.

consists of the altered blood, glandular secretion, and sloughed superficial endometrial tissue. The basal portion of the endometrium, with stubs of the uterine glands, remains intact because it has a conventional blood supply which is separate from that of the superficial layer.

A brief **postmenstrual phase** precedes the next proliferative phase. Even before menstrual discharge ceases, the epithelial cells of the uterine gland stubs in the basal layer proliferate and move out to reestablish a surface epithelium. The endometrium is only about one-sixth as thick as it was at the progravid phase.

Achievement of pregnancy is the goal of the female reproductive organs. It may be illogical to stop our consideration of the endometrium short of this goal; but the story of implantation and formation of an embryo is long, and there is no good stopping place once we start. Therefore, we shall leave all of that to courses in embryology. There are several good textbooks of the subject, some of which are listed in the bibliography (page 433). Figure 280 illustrates marked glandular proliferation in the endometrium of the early gravid stage.

The **cervix uteri** differs markedly from the rest of the uterus in respect to its mucous membrane. The surface epithelium is simple columnar, made up of tall, pale-staining mucous cells. Glands are large branched tubular structures, formed by tall cells like those of the surface. They are shown in Fig. 281. No cyclical changes occur in the mucous membrane of the cervix. The lumen opens onto the vaginal portion of the uterus, which is covered with stratified squamous epithelium continuous with that lining the vagina.

The **myometrium** is a thick tunic consisting of a number of layers of large smooth-muscle fibers interspersed with fibrous connective tissue carrying blood vessels, lymphatics, and nerves. It is illustrated in the low-power photomicrograph shown in Fig. 277A. The myometrial connective tissue contains few elastic fibers except in the region of the cervix. Muscle cells undergo some hypertrophy during the progravid phase of the endometrium and diminish again in size after menstruation. They attain phenomenal length during pregnancy.

Postmenopausal uterus: When estrogenic stimuli are no longer provided by ripening ovarian follicles, the uterus ceases to exhibit its characteristic cycles. After the menopause, the endometrium undergoes atrophic change. Uterine glands become short and fewer in number. They often appear cystic, as in Fig 278C. Fibrous connective tissue increases in amount in the myometrium, and abnormal fibrous tumors

are not uncommon. The cervix loses prominence in old age and recedes, as it were, from its protrusion into the vagina.

FIGURE 282 Human vagina, showing stratified squamous epithelium on papillae of fibrous connective tissue containing many leucocytes Venous channels (v) can be seen in the heavy lamina propria The muscular layers are indicated (m), below them a fibrous adventitia is shown Photomicrograph, 40 ×.

VAGINA

The vagina is a tubular organ connecting the uterus with the exterior and providing a receptacle for the semen at coitus. It is a flat channel lined with stratified squamous epithelium and surrounded by fibrous connective tissue and smooth muscle (Fig. 251).

The epithelium of the vagina rests upon a well-marked papillary layer

FIGURE 283 Human vaginal mucosa This is a detail from the same specimen as Fig 282 Note the cellular lamina propria and many small venous channels Photomicrograph, 150 ×

of lamina propria, rich in blood vessels and containing lymphocytes. There are no glands, as a rule, the mucosa is moistened by secretions from the uterus. Figures 282 and 283 illustrate the structure of the vagina.

The thickness of the vaginal epithelium varies with age, for it is influenced by the estrogenic hormone. At birth it is thick because the mother's estrogen has acted through the placenta. Within two weeks after birth, the vaginal epithelium of the infant becomes a thin layer and remains so until estrogens are secreted by the ovary after puberty. Again, after menstrual cycles cease at the menopause, the vaginal epithelium becomes thin.

The secretions of the uterus which moisten the vaginal mucosa contain glycogen from the uterine glands. Bacterial fermentation of glycogen produces acid in the vagina, most marked during the progravid phase. If it were not for seminal alkalinity and buffering action, sperm would die in the vagina before accomplishing their mission.

The tunica muscularis of the vagina lies external to the mucosa, there being no distinct submucous layer. The division into inner circular and outer longitudinal layers is quite indistinct. Much fibrous connective tissue is interspersed among the smooth-muscle bundles. A circular vaginal sphincter of skeletal-muscle fibers guards the external orifice.

EXTERNAL GENITALIA

The **labia minora** are folds of thin skin, merging with the mucous membrane of vestibule and vaginal orifice. Hair follicles and fat cells are absent, sebaceous glands, sweat glands, and nerves are present.

The **vestibule** lies between the labia minora. Paraurethral glands, homologues of the prostate, may empty onto the mucous membrane of the vestibule. So do the ducts of the large **vestibular glands** (Bartholin), which are homologues of the male bulbourethral glands. They are tubulo-alveolar glands, each with a main duct lined with simple columnar epithelium. All these glands secrete mucus.

The **clitoris** is formed of two miniature erectile bodies corresponding to the corpora cavernosa penis. It also has rudimentary homologues of the glans and corpus cavernosum urethrae of the male. The clitoris is covered by a mucous membrane continuous with that of the vestibule.

The **labia majora** are large folds of skin with hair follicles, sweat glands, and sebaceous glands. The hair follicles are especially well developed on the outer surface. Subcutaneous fat, a few smooth-muscle fibers, a venous plexus, and loose connective tissue are to be found in the labia majora. These bodies are homologues of the two halves of the scrotum.

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   This is a splendid description of menstrual cyclic changes, with good illustrations. A study of other primates is reported in the same volume on page 353.

2. Bartelmez, G. W.: Female Genital System, being Chap. 25, pp. 542–590, in *A Textbook of Histology*, 5th ed., A. A. Maximow and W. Bloom; Philadelphia, W. B. Saunders Company, 1948.
   There are some good illustrations, especially those on the gravid uterus, in this account.

3. Corner, G. W.: Cytology of the Ovum, Ovary and Fallopian Tube, being Chap. 39, vol. 3, pp. 1567–1607, in *Special Cytology*, 2d ed., E. V. Cowdry, editor; New York, Paul B. Hoeber, Inc., 1932.
   Although not the most recent article, this is brief, well illustrated, and easily read.

Mammary Glands

The mammary glands or breasts are modified apocrine sweat glands. Each is formed by about twenty irregular lobes, each of which opens onto the nipple by one lactiferous duct. The lobes radiate outward from the nipple and are embedded in adipose and fibrous connective tissue of the superficial fascia. The whole organ is covered with thin skin, which assumes special characteristics at the areola around the nipple.

Lactiferous ducts: Simple columnar epithelium, rather tall in most places and having patches of the pseudostratified type here and there, lines the **lactiferous ducts**. Toward the nipple, the epithelium becomes stratified squamous. The ducts end in small pores upon the nipple. In their course, they are much wider than their openings and their walls are folded longitudinally. A dilatation in each duct, called a **lactiferous sinus**, occurs near the base of the nipple. The epithelium of the duct rests upon a basement membrane, and much of its subepithelial connective tissue is arranged circularly.

Parenchyma and stroma: The structure of the mammary gland differs with advance in age and with changing functional stages. The periods during which its structure should be considered are early postnatal, childhood, adolescence, adult resting stage, gestation and lactation, regression, and involution.

During the **postnatal period**, *i.e.*, the early days or even weeks after birth, each branching lactiferous duct divides into small tubules which are dilated at their ends to form alveoli. These are lined with simple columnar epithelium in which secretory activity may be observed. The alveoli and ducts contain some of the secretion; free cells are present in the secretion as they are at the beginning of lactation in the adult gland. Figure 284 illustrates the structure during this period. The glands of both

REFERENCES

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   metrium of Rhesus Monkey, Baboon, Chimpanzee and Gibbon, *Anatomi-
   cal Record*, vol. 99, pp. 199–225, 1947.
   *This is a splendid description of menstrual cyclic changes, with good il-
   lustrations. A study of other primates is reported in the same volume on
   page 353.*

2. Bartelmez, G. W.: Female Genital System, being Chap. 25, pp. 542–590,
   in *A Textbook of Histology*, 5th ed., A. A. Maximow and W. Bloom;
   Philadelphia, W. B. Saunders Company, 1948.
   *There are some good illustrations, especially those on the gravid uterus, in
   this account.*

3. Corner, G. W.: Cytology of the Ovum, Ovary and Fallopian Tube, being
   Chap. 39, vol. 3, pp. 1567–1607, in *Special Cytology*, 2d ed., E. V.
   Cowdry, editor; New York, Paul B. Hoeber, Inc., 1932.
   *Although not the most recent article, this is brief, well illustrated, and
   easily read.*

FIGURE 285. Mammary gland of a nonpregnant adult woman. In this resting stage, the branching tubules occupy islands of loose fibrous connective tissue. Photomicrograph, 150 ×.

only about 10 mm. in diameter. Each lobule consists only of fully developed ducts with blind ends and no secreting epithelium. They are embedded in connective tissue beneath the nipple.

FIGURE 284. Mammary gland with lactiferous ducts; from a human infant soon after birth. The gland still shows some of the hypertrophy induced by maternal hormone. Photomicrograph, 150 ×.

sexes present the same appearance; both have been stimulated through placental passage of the mother's hormone.

During **childhood,** the glands of both sexes are similar. They measure

FIGURE 285. Mammary gland of a nonpregnant adult woman. In this resting stage, the branching tubules occupy islands of loose fibrous connective tissue. Photomicrograph, 150 ×.

only about 10 mm. in diameter. Each lobule consists only of fully developed ducts with blind ends and no secreting epithelium. They are embedded in connective tissue beneath the nipple.

The **adolescent** male gland retains its involutional childhood state. No development of alveoli occurs, although it may measure 2 cm. in diameter in the adult.

The female gland begins to enlarge a little before puberty, when the areola becomes elevated. Growth of the duct system, reappearance of alveoli, and accumulation of fat between glandular lobes gradually develop the breast during adolescence. Such growth comes about cyclically and *is stimulated by the newly functioning ovaries.*

The **resting adult** mammary gland, before the first pregnancy, consists of many groups of branching tubules or cords of cells and immature alveoli connected with each lactiferous duct. These are embedded in islands of loose intralobular connective tissue, more cellular than that forming the main stroma of the breast (Fig. 285). The ducts and alveoli are lined with low simple columnar epithelium resting on a basement membrane and clasped by myoepithelial cells, much like those of sweat glands.

With the advent of **pregnancy,** marked changes culminating in lactation take place. Terminal ducts and alveoli greatly increase in number. Alveoli grow in size. Groups of them crowd the intralobular connective tissue so that it becomes no longer visible. The coarser connective tissue forms capsules for the lobules of the gland. The skin over the gland becomes stretched.

Columnar epithelial cells of the alveoli display droplets of secretion in their cytoplasm during the *eighth month of gestation.* These droplets run together to form larger drops near the outer pole of the cells. They are extruded by bulging from the free surface and pinching off a little of the cytoplasm as they enter the lumen. Macrophages make their way into the lumen of alveoli and phagocytize some of the droplets of secretion. The macrophages become much enlarged and are known as **colostrum corpuscles.** Ducts and the lactiferous sinuses fill with milk containing these corpuscles and other cells and cell fragments.

Active **lactation** begins after labor. It is stimulated by a hormone from the *anterior lobe of the hypophysis.* The first secretion is called **colostrum.** Fat content of the mammary gland secretion soon increases and true milk replaces colostrum Secretion takes place at different times in different alveoli. Each alveolus undergoes periods of secretion alternating with periods of inactivity. During lactation, the gland is made up very largely of hypertrophied alveoli, and the connective tissue is reduced in amount. Figure 286 shows the lactating gland.
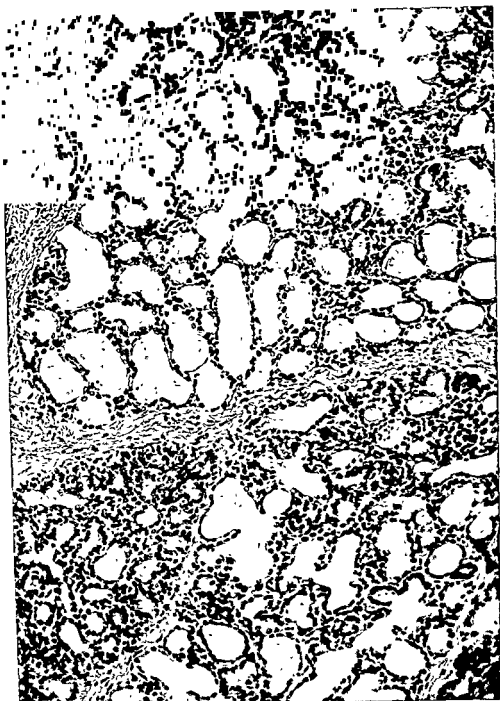
FIGURE 286. Lactating mammary gland, showing portions of several lobules in different stages of secretory activity Photomicrograph, 150 ×.

Regression is a gradual process. After the nursing period is over, the alveoli cease to function and become reduced in size and number, some remaining for a considerable time. Few remain until the next pregnancy.

The intralobular connective tissue reappears, and the interlobular connective tissue and fat increase in amount.

FIGURE 287 Atrophic mammary gland of a 66-year-old woman. The tubules are surrounded by dark (acidophilic) bands, the remnants of intralobular connective tissue. Interlobular connective tissue is dense and shows much artifactual shrinkage. Specimen by Prof. R. F. Becker. Photomicrograph, 150 ×.

Involution of the mammary gland occurs after the menopause. This, too, is gradual. The alveoli disappear, the lobes diminish in size, and the ducts become atrophic. Thus, there is a trend toward the prepubertal structure in old age. The condition seen in Fig. 287 is one of advanced atrophy.

The mammary glands are well supplied by blood vessels. Arteries are derived from several sources. Veins form a superficial plexus, which becomes especially prominent during lactation. The lymphatics of the mammary gland are numerous and of great importance. The distribution of lymphatics, vessels, and nerves is considered in textbooks of gross anatomy.

NIPPLE AND AREOLA

The nipple and areola are formed by a special thin skin. The corium of the nipple invaginates the epidermis with many vascular papillae. Hair and sweat glands are absent, but sebaceous glands are numerous and provide a saliva-resisting lubricant which is useful during nursing. Deep layers of the corium contain smooth muscle arranged circularly and vertically. The areola is pigmented, especially in dark-complexioned women. Pigmentation increases with the advent of pregnancy and decreases afterward. Fat is absent from the corium of the areola and the nipple. Areolar glands were considered on page 254.

REFERENCE

1. Bunting, H.: Cytochemical Properties of Apocrine Sweat Glands Normally Present in the Human Mammary Gland. *Anatomical Record*, vol. 101, pp. 5–12, 1948.

Read this for an interesting side light on the subject of the mammary gland

The intralobular connective tissue reappears, and the interlobular connective tissue and fat increase in amount.

FIGURE 287. Atrophic mammary gland of a 66-year-old woman. The tubules *are surrounded by dark (acidophilic) bands, the remnants of intralobular con-nective tissue.* Interlobular connective tissue is dense and shows much artifactual shrinkage. Specimen by Prof. R. F. Becker. Photomicrograph, 150 ×.

Involution of the mammary gland occurs after the menopause. This, too, is gradual. The alveoli disappear, the lobes diminish in size, and the ducts become atrophic. Thus, there is a trend toward the prepubertal structure in old age. The condition seen in Fig. 287 is one of advanced atrophy.

TABLE 2. Units of Length

Metric	English
1 meter or 100 centimeters (cm.)	3 feet (ft.), 3¼ inches (in.)
1 centimeter (cm.) or 10 millimeters (mm.)	⅖ inch (in.)
1 millimeter (mm.) or 1,000 microns (μ)	½₅ inch (in.)
1 micron (μ) or 1,000 millimicrons (mμ)*	½₅,₄₀₀ inch (in)

* A smaller unit of measurement is the angstrom ($\overset{\circ}{A}$)—0.1 millimicron, or ½₅₄,₀₀,₀₀₀ inch —which is used for wave lengths.

EXAMPLES

A 6-foot, 6¾-inch man would be 2 meters tall.

At birth he was 20 inches long, or 50 centimeters.

His hand[1] is approximately 4 inches wide, or 10 centimeters.

Each of his red blood corpuscles is about 7.5 microns in diameter.

Bacteria, with which he is constantly associated, are in the range of 1 micron, viruses measure about 0 1 micron.

TABLE 3. Units of Volume

Metric	Apothecaries' Wine Measure
1 liter (l.) or 1,000 cubic centimeters (cc)	1 06 quarts (qt) or 2 11 pints (pt.)
1 cubic centimeter (cc.)* or 1,000 cubic millimeters (cu mm.)	0 034 fluid ounces (fl. oz) or 0 27 fluid drams (fl. d)
1 cubic millimeter (cu mm)	0 016 minim (min)†

* One cubic centimeter (cc.) is the same as 1 milliliter (ml.); 1 cc. of distilled water weighs 1 gm. at 4°C

† A minim, or drop, is ½₀ fluid dram.

[1] A hand is a unit of measurement used in reference to the height of horses.

Units of Measurement Used in Histology

The metric system is universally used in fields of science. Probably you are familiar with meters, kilograms, and liters, but the chances are that you think in terms of yards, pounds, and quarts and have to translate the metric units into those of every day life. The following brief tables of approximate equivalents and some examples are printed here to help you understand the metric terms that exclusively appear in this book.

TABLE 1. Units of Weight

Metric	Avoirdupois
1 kilogram (kg.) or 1,000 grams (gm.)	2 pounds (lb.), 3¼ ounces (oz.)
1 gram (gm.) or 1,000 milligrams (mg)	0.035 ounces (oz.) 15 43 grains (gr.)
1 milligram (mg.) or 1,000 micrograms (mmg)	0 015 grains (gr.)

EXAMPLES

A man weighs 165 pounds or 75 kilograms.
His heart weighs 10½ ounces or 300 grams.
His hypophysis weighs only 9 grains or 600 milligrams.
He began life as an ovum 0.1 millimeter in diameter, weighing 0.5 microgram.

General Reference Books in English Used in Preparation of This Textbook

Addison, W. H. F.: *Piersol's Normal Histology, with Special Reference to the Structure of the Human Body*, 15th ed.; Philadelphia, J. B. Lippincott Company, 1932.

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Hamilton, W. J., J. D. Boyd, and H. W. Mossman *Human Embryology (Prenatal Development of Form and Function)*, Baltimore, The Williams & Wilkins Company, 1945.

EXAMPLES

A 75-kilogram man has about 12¾ pints, or 6 liters, of blood.
The capacity of his cranial cavity is 1.5 liters.
His urinary bladder has a capacity of 1 pint, or 500 cubic centimeters.
His gall bladder capacity is 13½ fluid drams or 50 cubic centimeters.

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Addison, W. H. F : *Piersol's Normal Histology, with Special Reference to the Structure of the Human Body*, 15th ed.; Philadelphia, J. B Lippincott Company, 1932.

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Windle, W. F.: *Physiology of the Fetus. Origin and Extent of Function in Prenatal Life*; Philadelphia, W. B. Saunders Company, 1940.

Visual Aids

Much can be accomplished toward presenting concepts of living cells and tissues by means of motion pictures. Not many laboratories are equipped to set up in vitro or in vivo experiments for the benefit of beginning students, and motion pictures offer good substitutes. Fortunately, some excellent films are available at small rentals or can be purchased for little more than the cost of reproduction. Reference has been made to a number of these throughout this textbook. Others are listed in pamphlets obtainable from the Wistar Institute of Anatomy in Philadelphia and the American College of Surgeons in Chicago.

The following list is comprehensive rather than selective. Each film should therefore be previewed before using, as some may contain information that is too advanced while others may contain information that is too elementary. Each film has been listed once in connection with the chapter to which it is most applicable. In many cases, however, it might be used advantageously in other chapters.

These films can be obtained from the producers or distributors whose addresses are given at the end of the list. In many instances they can be obtained from your local film library or local film distributor; also, some universities have large film libraries from which they can be borrowed, bought, or rented. All the films are 16mm, black and white, with the one exception noted. The running time (min) and whether it is silent (si) or sound (sd) are listed with each title.

CHAPTER 2—CELLS, LIVING COMPONENTS OF TISSUES

1. *Dividing Normal Adult Rat Fibroblasts in Vitro* (Wistar 4min si). W. H. Lewis. Mitotic division in fibroblasts as seen in tissue culture preparations of cells derived from adult rat tissue.
2. *Dividing Cancer Cells in Vitro* (Wistar 4min si). W. H. Lewis and M. R. Lewis. Mitotic divisions of cells in tissue cultures grown from tissue taken from tumors.
3. *Pinocytosis; Drinking by Cells* (Wistar 10min si). W. H. Lewis. Cytoplasmic activity of cells grown in tissue cultures.
4. *Protoplasm—The Beginning of Life* (Bray 15min si). Movement, irritability, assimilation, and reproduction of ameba, stentor, etc.
5. *The Amoeba* (United 10min sd). Structure and function of ameba; illus-

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trates study of protoplasm and cells including energy relations, response to stimuli, and reproduction.

6. *Normal and Abnormal White Blood Cells in Tissue Cultures* (Wistar 15min si). W. H. Lewis and others. Various types of normal leucocytes in movement, bringing out differences in mode of progression.

7. *Tumor Cells and Macrophages in Tissue Cultures. Rat Sarcomas and Carcinomas* (Wistar 13min si). W. H. Lewis. Behavior, in tissue cultures, of cells derived from variety of rat sarcomas and carcinomas, all taken with time-lapse apparatus.

8. *The Cultivation of Living Tissue* (Am. Cancer Soc. 20min si). R. C. Canti. Produced in 1928; now old and in poor condition.

CHAPTER 4—BLOOD

9. *Effects of Heat and Cold on the Circulation of the Blood* (A. M. A. 8min si). E. R. Clark. Photographed through the microscope, showing vessels in the rabbit-ear chamber.

10. *Micromanipulative Studies of Blood Capillaries* (Wistar 15min si). B. W. Zweifach. Circulation of blood under the microscope.

11. *Blood* (EBF 12min si). Separation of plasma from blood cells; protein and salts from plasma; staining cells; counting red blood corpuscles; how white blood cells reach body tissue; clotting of blood.

CHAPTER 7—CARTILAGE, BONE, AND JOINTS

12. *Body Framework* (EBF 15min si). Function of skeleton, structure, chemical composition, growth, and repair of bones, main types of joints.

CHAPTER 8—MUSCULAR TISSUE

13. *Muscles* (EBF 15min si). Structure and use of muscles.

14. *Activity of Heart Muscle from Rat Embryos, Grown in Tissue Cultures* (Wistar 15min si). C. M Goss. Contraction of cardiac muscle fibers.

CHAPTER 9—HEART

15. *The First Heartbeats and the Beginning of the Circulation of Blood* (U. of Mich. 30min si). B. M. Patten and T. C. Kramer. Embryological study, using the chick.

16. *Heart and Circulation* (EBF 11min sd). Mechanics of pulmonary and systemic systems with delineation of heart action; microscopic scenes of capillary action.

17. *The Human Heart* (Brandon 10min sd). Mechanics and functions of the heart.

CHAPTER 10—BLOOD VESSELS AND LYMPHATICS

18. *Effects of Massage on the Circulation of the Blood* (A. M. A. 8min si). E. R. Clark.

19. *Circulatory Control* (EBF 15min si). Pressure of blood in arteries; methods of measuring blood pressure; structure and work of veins.

20. *Contraction of Arteries and Arteriovenous Anastomoses* (A. M. A. 12min si). E. R. Clark. Observations in vivo, using the rabbit-ear chamber technique.

21. *Control of Small Blood Vessels* (Lutz 20min si). G. P. Fulton and B. R. Lutz. Structural and physiological features of arterioles, precapillaries, and capillaries.

CHAPTER 11—LYMPHATIC TISSUE AND ORGANS

22. *Mesenteric Lymphatics, Their Conduct and the Behavior of Their Valves in the Living Rat* (Wistar 15min si). R. L. Webb. Contractility of the mesenteric lymphatics in the rat.

CHAPTER 12—NERVOUS TISSUE AND THE PERIPHERAL NERVOUS SYSTEM

23. *Growth of Nerve Fibers* (U. of Vir. 16min si). C. C. Speidel. A number of other excellent films are available from the same source.

24. *Development of the Nervous System* (Northwestern 16min si). J. J. McDonald. Structure of nervous system; its pathways and connections; nature of nerve impulse.

25. *Reflex Action* (Brandon 15min si). Structure of neuron, path of an impulse, and definition of reflex act.

CHAPTER 13—BRAIN AND SPINAL CORD

26. *The Spinal Cord* (Brandon 30min si). Complete structure and functions of spinal cord.

27. *Neurons and Neuroglia in Tissue Cultures* (Wistar 16min si). W. H. Lewis. A new film which has not as yet been titled.

28. *The Brain* (Brandon 75min si). Structure; cranial nerves, embryonic development, ventricles, fissures and convolutions, cerebral hemispheres.

CHAPTER 15—VISUAL AND AUDITORY ORGANS

29. *How the Eye Functions* (Knowledge Bldrs 15min sd). J. R. McCrory Studios. Functions of various parts of eye, shown by diagrammatic drawings.

30. *How the Ear Functions* (Knowledge Bldrs 11min sd). J. R. McCrory Studios. Structure and function of human ear.

CHAPTER 16—INTEGUMENT

31. *Skin* (EBF 15min si). C. E. Turner. Skins of various animals; human skin, its structure, growth of cells; secretion of sweat; structure of hair and nails.
32. *The Human Hair* (Bray 11min sd). Hair as part of skin; growth of hair within follicle; various characteristics of hair.

CHAPTER 17—MOUTH AND PHARYNX

33. *How Teeth Grow* (EBF 15min si). Development of teeth, showing structure and arrangement; structure of a tooth and blood vessels which surround it.
34. *Human Throat* (Bray 12min sd). Throat described from anatomical and functional aspects.

CHAPTER 18—TUBULAR DIGESTIVE ORGANS

35. *Development of the Gastro Intestinal Tract* (Columbia 60min si). Embryology of tract.
36. *Anomalies in the Development of the Gastro-intestinal Tract* (Columbia 20min si). Preoperative and operative findings explained.
37. *Digestion of Foods* (EBF 11min sd). A. J. Carlson and H. G. Swann. Summary of digestive process, including work performed in mouth, stomach, and small intestine; relation of circulatory and nervous systems to digestive process.
38. *Alimentary Tract* (EBF 11min sd). Intended as supplement to *Digestion of Foods*. Motility phenomena of gastrointestinal tract.

CHAPTER 20—ENDOCRINE ORGANS

39. *Endocrine Glands* (EBF 11min sd). A. J. Carlson and H. G. Swann. Effects of improper functioning of the glands; causes and remedies of faulty glandular actions.

CHAPTER 21—RESPIRATORY ORGANS

40. *Mechanisms of Breathing* (EBF 11min sd). V. Johnson. Breathing mechanism in operation; technical animation of gaseous exchange in lungs and body tissue cells.

CHAPTER 22—EXCRETORY ORGANS

41. *Work of the Kidneys* (EBF 11min sd). A. J. Carlson and others. Detailed exposition of kidneys and their functions.

42. *Kidneys, Ureters and Bladder* (Bray 11min sd). Important anatomical features of kidneys, ureters, and urinary bladder.

CHAPTER 23—MALE REPRODUCTIVE ORGANS

43. *Technic for Counting Motile Spermatozoa* (Wistar 15min si). E. J. Farris. Variations in morphology and behavior of human spermatozoa.

CHAPTER 24—FEMALE REPRODUCTIVE ORGANS

44. *Ovulation in the Rabbit* (Yale 8min si). R. T. Hill, Edgar Allen, and T. C. Kramer. The rupture of ovarian follicles and the liberated ova.

45. *Forming an Egg* (Kansas 15min sd). D. C. Warren and H. M. Scott. A color film.

46. *Ovulation in the Ewe* (Mo 8min si). F. F. McKenzie and C. E. Terrill. No microscopic views.

SOURCES OF FILMS LISTED ABOVE

Am. Cancer Soc.—American Cancer Society Inc., 47 Beaver St , New York 4

A. M. A.—American Medical Association, Committee on Motion Pictures, 535 N. Dearborn Street, Chicago 10, Ill.

Brandon—Brandon Films Inc., 1600 Broadway, New York 19

Bray—Bray Studios Inc., 729 Seventh Ave., New York 19

Columbia—Columbia University Educational Films, Columbia University, New York 27

EBF—Encyclopaedia Britannica Films Inc., 1150 Wilmette Ave., Wilmette, Ill.

Kansas—Poultry Dept., Kansas State College, Manhattan, Kans.

Knowledge Bldrs—Knowledge Builders, 625 Madison Ave., New York 22

Lutz—Dr. Brenton R. Lutz, 675 Commonwealth Ave., Boston, Mass.

Mo—Animal Husbandry Department, University of Missouri, Columbia, Mo.

Northwestern—Dr. L. B. Arey, Northwestern University Medical School, Chicago, Ill

U. of Mich.—Dr. B. M. Patten, Dept. of Anatomy, University of Michigan, Ann Arbor, Mich.

U. of Vir—Dr C. C. Speidel, School of Anatomy, University of Virginia, Charlottesville, Va.

United World Films Inc., 1445 Park Ave., New York 29

Wistar—Wistar Institute of Anatomy and Biology, 36th St. and Woodland Ave., Philadelphia 4, Pa.

Yale—Dr. W. U. Gardner, Dept. of Anatomy, Yale University Medical School, New Haven, Conn.

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